Health Canada Santé Canada

Your health and safety... our priority. Votre santé et votre sécurité... notre priorité.

Proposed Registration Decision PRD2015-02

Bicyclopyrone

(publié aussi en français)

13 February 2015

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6607 D
Ottawa, Ontario K1A 0K9

Internet: pmra.publications@hc-sc.gc.ca
healthcanada.gc.ca/pmra
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra.infoserv@hc-sc.gc.ca

Canada

ISSN: 1925-0878 (print)
1925-0886 (online)

Catalogue number: H113-9/2015-2E (print version)
H113-9/2015-2E-PDF (PDF version)

© Her Majesty the Queen in Right of Canada, represented by the Minister of Health Canada, 2015

All rights reserved. No part of this information (publication or product) may be reproduced or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, or stored in a retrieval system, without prior written permission of the Minister of Public Works and Government Services Canada, Ottawa, Ontario K1A 0S5.

Table of Contents

Overview 1
  Proposed Registration Decision for Bicyclopyrone 1
  What Does Health Canada Consider When Making a Registration Decision? 1
  What Is Bicyclopyrone? 2
  Health Considerations 3
  Environmental Considerations 5
  Value Considerations 6
  Measures to Minimize Risk 6
  Next Steps 7
  Other Information 7
Science Evaluation 9
1.0 The Active Ingredient, Its Properties and Uses 9
  1.1 Identity of the Active Ingredient 9
  1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product 10
  1.3 Directions for Use 12
    1.3.1 SYNA16003 Herbicide 12
    1.3.2 Acuron Herbicide 12
  1.4 Mode of Action 13
2.0 Methods of Analysis 13
  2.1 Methods for Analysis of the Active Ingredient 13
  2.2 Method for Formulation Analysis 13
  2.3 Methods for Residue Analysis 13
3.0 Impact on Human and Animal Health 14
  3.1 Toxicology Summary 14
    3.1.1 *Pest Control Products Act* Hazard Characterization 18
  3.2 Acute Reference Dose 18
  3.3 Acceptable Daily Intake 19
  3.4 Occupational and Residential Risk Assessment 20
    3.4.1 Toxicological Endpoints 20
    3.4.2 Occupational Exposure and Risk 21
    3.4.3 Residential Exposure and Risk Assessment 24
  3.5 Food Residues Exposure Assessment 24
    3.5.1 Residues in Plant and Animal Foodstuffs 24
    3.5.2 Drinking Water 24
    3.5.3 Dietary Risk Assessment 27
    3.5.4 Aggregate Exposure and Risk 28
    3.5.5 Maximum Residue Limits 28
4.0 Impact on the Environment 29
  4.1 Fate and Behaviour in the Environment 29
  4.2 Environmental Risk Characterization 30
    4.2.1 Risks to Terrestrial Organisms 31
    4.2.2 Risks to Aquatic Organisms 33
    4.2.3 Incident Reports or Special Use Pattern 35
5.0 Value 35

5.1 Effectiveness Against Pests ... 35
5.1.1 Acceptable Efficacy Claims for SYNA16003 Herbicide ... 35
5.1.2 Acceptable Efficacy Claims for Acuron Herbicide ... 36
5.1.3 Herbicide Tank Mix Combinations ... 36
5.2 Non-Safety Adverse Effects ... 37
5.2.1 SYNA16003 Herbicide ... 37
5.2.2 Acuron Herbicide ... 37
5.2.3 Impact on Succeeding Crops ... 38
5.3 Consideration of Benefits ... 38
5.3.1 Social and Economic Impact ... 38
5.3.2 Survey of Alternatives (as of January 2014) ... 38
5.3.3 Compatibility with Current Management Practices Including Integrated Pest Management ... 40
5.3.4 Information on the Occurrence or Possible Occurrence of the Development of Resistance ... 40
5.4 Supported Uses ... 41
6.0 Pest Control Product Policy Considerations ... 41
6.1 Toxic Substances Management Policy Considerations ... 41
7.0 Summary ... 43
7.1 Human Health and Safety ... 43
7.2 Environmental Risk ... 44
7.3 Value ... 45
8.0 Proposed Regulatory Decision ... 45
List of Abbreviations ... 47
Appendix I Tables and Figures ... 49
Table 1 Residue Analysis ... 49
Table 2 Toxicity Profile of End-Use Products Containing Bicyclopyrone ... 53
Table 3 Toxicity Profile of Technical Bicyclopyrone ... 54
Table 4 Toxicology Endpoints for Use in Health Risk Assessment for Bicyclopyrone ... 65
Table 5 Integrated Food Residue Chemistry Summary ... 66
Table 6 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment .. 86
Table 7 Fate and Behaviour in the Environment ... 88
Table 8 Bicyclopyrone and Its Transformation Products ... 98
Table 9 Effects on Non-Target Species ... 101
Table 10 Screening Level Risk Assessment on Aquatic and Terrestrial Non-Target Species Excluding Birds and Mammals ... 103
Table 11 Screening Level Risk Assessment on Non-Target Species for Birds and Small Wild Mammals ... 105
Table 12 Expanded Screening Level Risk Assessment for Birds ... 106
Table 13 Expanded Screening Level Risk Assessment on Reproduction of Small Wild Mammals ... 107
Table 14 Use (label) Claims Proposed by Applicant and Whether Acceptable or Unsupported ... 109
Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications ... 113
References ... 115

Overview

Proposed Registration Decision for Bicyclopyrone

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Bicyclopyrone Technical, the manufacturing concentrate products Bicyclopyrone Wet Paste I and Bicyclopyrone Wet Paste II, and the end-use product SYNA16003 Herbicide, containing the technical grade active ingredient bicyclopyrone, to control specific weeds in field, sweet and seed corn. Also proposed for full registration is Acuron Herbicide, containing the active ingredients bicyclopyrone, atrazine, s-metolachlor and mesotrione to control specific weeds in field, sweet and seed corn.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Bicyclopyrone Technical, Bicyclopyrone Wet Paste I, Bicyclopyrone Wet Paste II, SYNA16003 Herbicide and Acuron Herbicide.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

---

[1] "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

[2] "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of the Health Canada website.

Before making a final registration decision on bicyclopyrone, the PMRA will consider all comments received from the public in response to this consultation document[3]. The PMRA will then publish a Registration Decision[4] on bicyclopyrone, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Bicyclopyrone?

Bicyclopyrone is a Group 27 Herbicide. It acts in susceptible plants by inhibiting the biosynthesis of carotenoids and leading to the destruction of chlorophyll. The mode of action of bicyclopyrone is shared with several other commercial herbicide active ingredients, specifically, mesotrione, isoxaflutole, topramezone, tembotrione and pyrasulfatole. Bicyclopyrone is efficacious against select broadleaf weeds as well as proso millet (a difficult to control grassy weed).

SYNA16003 Herbicide contains the active ingredient bicyclopyrone at 200 grams per litre of product and Acuron Herbicide contains bicyclopyrone at 7.1 grams, mesotrione at 28.5 grams, atrazine at 120 grams and s-metolachlor at 257 grams per litre of product.

---

[3] “Consultation statement” as required by subsection 28(2) of the *Pest Control Products Act*.

[4] “Decision statement” as required by subsection 28(5) of the *Pest Control Products Act*.

Health Considerations

Can Approved Uses of Bicyclopyrone Affect Human Health?

Products containing bicyclopyrone are unlikely to affect your health when used according to label directions.

Potential exposure to bicyclopyrone may occur through the diet (food and water) or when handling and applying the products. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products containing bicyclopyrone are used according to label directions.

In laboratory animals, the technical grade active ingredient bicyclopyrone was of low acute toxicity by the oral, dermal and inhalation routes. Bicyclopyrone was minimally irritating to the eye, non-irritating to the skin, and did not cause an allergic skin reaction.

The end-use product, SYNA16003 Herbicide was of low acute toxicity via the oral, dermal and inhalation routes. It was non-irritating to the skin and minimally irritating to the eyes. SYNA16003 Herbicide caused an allergic skin reaction; consequently, the hazard statement "POTENTIAL SKIN SENSITIZER" is required on the label for this end-use product.

The end-use product, Acuron Herbicide was slightly acutely toxic via the oral route, was of low acute toxicity via the dermal and inhalation routes and minimally irritating to the eye. It was moderately irritating to the skin and caused an allergic skin reaction. Based on the above findings, the signal words and hazard statements "WARNING, POISON, SKIN IRRITANT and POTENTIAL SKIN SENSITIZER" are required on the label.

There was some indication that bicyclopyrone caused damage to the nervous system in dogs only. There were no effects on the immune system. Health effects in animals given repeated doses of bicyclopyrone included effects on the liver, kidney, eyes, and on body weight (bw). There was no evidence to suggest that bicyclopyrone damaged genetic material. Bicyclopyrone did, however, cause lung tumours in mice and eye tumours in rats.

When bicyclopyrone was given to pregnant or nursing animals, effects (malformations) on the developing fetus were observed at doses that were not toxic to the mother, indicating that the young were more sensitive to bicyclopyrone than the adult animal.

The risk assessment protects against the effects of bicyclopyrone by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and drinking water are not of health concern.

Aggregate dietary intake estimates (food plus drinking water) revealed that the general population and infants, the subpopulation which would ingest the most bicyclopyrone relative to body weight, are not expected to be exposed to greater than 100% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from bicyclopyrone is not of health concern for all subpopulations, including infants.

Bicyclopyrone is not carcinogenic; therefore, a cancer dietary risk assessment is not required.

Acute dietary (food plus drinking water) intake estimates for females 13 to 49 years old were 97% of the acute reference dose (ARfD), and is not of health concern. The general population and all other population subgroups were less than 1% of the ARfD, and are not of health concern.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted on corn (field, sweet and pop) throughout the United States, and on sugarcane in Australia using bicyclopyrone are acceptable. The MRLs for this active ingredient can be found in the Science Evaluation section of this consultation document.

Acuron Herbicide is formulated with the active ingredients mesotrione, atrazine, s-metolachlor and the safener benoxacor. These active ingredients are already registered for use in Canada.

Risks in Residential and Other Non-Occupational Environments

Occupational Risks From Handling SYNA16003 Herbicide and Acuron Herbicide

Occupational risks are not of concern when SYNA16003 Herbicide and Acuron Herbicide are used according to the proposed label directions, which include protective measures.

Farmers and custom applicators who mix, load and apply SYNA16003 Herbicide and Acuron Herbicide as well as field workers re-entering freshly treated fields can come in direct contact with bicyclopyrone residues on the skin. Therefore, the SYNA16003 Herbicide label specifies that anyone mixing/loading must use closed mixing and loading equipment, and must wear a long-sleeved shirt and long pants, chemical-resistant gloves, socks, shoes, and eye protection. During application, clean-up and repair, workers must wear coveralls over a long-sleeved shirt and long pants, socks, and shoes. In addition, workers must wear chemical-resistant gloves during clean-up, repair, or if contact with spray nozzles is necessary. The Acuron Herbicide label specifies that anyone mixing, loading or applying the herbicide, and during clean-up and repair, must wear coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, and shoes with socks. In addition, when mixing/loading, workers must wear a faceshield. Chemical-resistant gloves are not required during application. The label also requires that workers do not enter treated fields for 15 days after application of SYNA16003 Herbicide, and 12 days after application of Acuron Herbicide, for hand setting irrigation equipment. For all other tasks, do not enter treated fields for 12 hours after application. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, risks to these individuals are not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Bicyclopyrone Is Introduced Into the Environment?

When used according to the label directions, bicyclopyrone is not expected to pose an unacceptable risk to the environment.

SYNA16003 and Acuron Herbicides, containing bicyclopyrone, can enter non-target terrestrial and aquatic habitats through spray drift and can enter aquatic habitats through run-off and leaching when used as a foliar spray on forage, sweet and field corn. In the terrestrial environment bicyclopyrone breaks down and is not expected to persist or accumulate over time. Breakdown of the molecule occurs mainly through reacting with sunlight and soil microbial activities. Bicyclopyrone is soluble in water and can move through the soil profile, and potentially reach ground water. In aquatic environments, bicylopyrone breaks down more slowly in the aquatic environment but does not accumulate. It may break down more rapidly, however, in the presence of sunlight in clear, shallow water.

Bicyclopyrone is unlikely to enter the atmosphere and be transported to areas far removed from where it was applied.

Bicyclopyrone is not expected to accumulate in plant and animal tissues.

Bicyclopyrone presents a negligible risk to aquatic organisms and most terrestrial organisms including birds, mammals, earthworms, parasitoid arthropods and honeybees. When bicyclopyrone is used at the labelled application rates it could pose a risk to certain non-target terrestrial plants if they are exposed to high enough concentrations. Therefore, mitigation measures, such as spray buffer zones, are required in order to minimize potential exposure of non-target terrestrial plants and, thereby, risk to the environment. When bicyclopyrone is used in accordance with the label and the required risk reductions measures are applied, the reduced environmental exposure is deemed adequate and risks are considered to be acceptable. Hazard statements for aquatic organisms and non-target terrestrial plants are required on product labels.

Value Considerations

What Is the Value of SYNA16003 Herbicide and Acuron Herbicide?

Proso millet is a difficult-to-control annual grassy weed and chemical control options are limited in corn.

There are currently no herbicides registered for use in corn that have residual soil activity on proso millet. Furthermore, the use pattern for SYNA16003 Herbicide is such that multiple weed control "options" are available for growers, including a two-pass weed control system (residual soil application followed by a planned post-emergent application), a one-pass post-emergent system, which would combine the residual capabilities of bicyclopyrone with the burndown ability of a glyphosate tank-mix partner, or a one-pass pre-emergent or post-emergent system with Primextra II Magnum Herbicide (Reg. No. 25730) or Lumax EZ Herbicide (Reg. No. 30964). Accordingly, the flexibility available with the proposed use pattern will provide a certain level of value to users of SYNA16003 Herbicide.

The combination of four active ingredients in Acuron Herbicide yields a product that can provide season-long control of a number of broadleaf and grassy weeds as well as provide early season suppression of proso millet in field, seed and sweet corn.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of SYNA16003 Herbicide and Acuron Herbicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with SYNA16003 Herbicide and Acuron Herbicide on the skin or through inhalation of spray mists, the SYNA16003 Herbicide label specifies that anyone mixing/loading must use closed mixing and loading equipment, and wear a long-sleeved shirt and long pants, chemical-resistant gloves, socks, shoes, and eye protection. During application, clean-up and repair, workers must wear coveralls over a long-sleeved shirt and long pants, socks and shoes. In addition, workers must wear chemical-resistant gloves during clean-up, repair, or if contact with spray nozzles is necessary. The Acuron Herbicide label specifies that anyone mixing, loading or applying the herbicide, and during clean-up and repair, must wear coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, and shoes with socks. In addition, when mixing/loading, workers must wear a faceshield. Chemical-resistant gloves are not required during application. In addition, the Acuron Herbicide label contains a spray-drift reduction statement for exposure protection in areas of human habitation.

Environment

- Standard hazard statements for non-target organisms including aquatic organisms and non-target terrestrial plants.
- Standard statements to inform users of conditions that may favour runoff and leaching
- Spray buffer zones to protect habitats from drift
- A statement advising that bicyclopyrone could potentially reach groundwater, particularly in areas where soils are permeable and/or the depth to the water table is shallow.

Next Steps

Before making a final registration decision on bicyclopyrone, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision, and the Agency's response to these comments.

Other Information

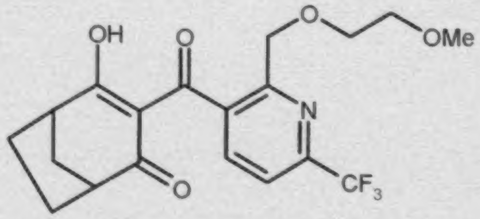
When the PMRA makes its registration decision, it will publish a Registration Decision on bicyclopyrone (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA Reading Room (located in Ottawa).

Science Evaluation

Bicyclopyrone

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active Substance	Bicyclopyrone
Function	Herbicide
Chemical Name	
1. International Union of Pure and Applied Chemistry (IUPAC)	4-hydroxy-3-{2-[(2-methoxyethoxy)methyl]-6-(trifluoromethyl)-3-pyridylcarbonyl}bicyclo[3.2.1]oct-3-en-2-one
2. Chemical Abstracts Service (CAS)	4-hydroxy-3-[[2-[(2-methoxyethoxy)methyl]-6-(trifluoromethyl)-3-pyridinyl]carbonyl]bicyclo[3.2.1]oct-3-en-2-one
CAS Number	352010-68-5
Molecular Formula	$C_{19}H_{20}F_3NO_5$
Molecular Weight	399.4
Structural Formula	
Purity of the Active Ingredient	99.3 %

1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

Technical Product—Bicyclopyrone Technical

Property	Result		
Colour and physical state	Yellow beige powder		
Odour	Weak, bitter odour		
Melting range	65.3°C		
Boiling point or range	Decomposes before boiling.		
Density	1.503 g/cm^3		
Vapour pressure at 20°C	$< 5 \times 10^{-6}$ Pa		
Ultraviolet (UV)-visible spectrum	**Solution**	**Wavelength (nm)**	**Molar Extinction Coefficient (L/mol × cm)**
	Neutral	238	11049
		272	13010
		295	9107
	Acidic	229	10854
		276	12994
		295	8919
	Basic	254	20670
		295	10114
Solubility in water at 25°C	**pH**	**Solubility (g/L)**	
	4.9	38	
	7.2	119	
	9.2	119	
Solubility in organic solvents at 25°C	**Solvent**	**Solubility (g/L)**	
	Acetone	> 500	
	Dichloromethane	> 500	
	Ethyl Acetate	> 500	
	Methanol	> 500	
	Toluene	> 500	
	Octane	91	
	Heptane	9	
n-Octanol-water partition coefficient (K_{ow})	**pH**	**log K_{ow}**	
	5	0.25	
	7	-1.2	
	9	-1.9	
Dissociation constant (pK_a)	3.06		
Stability (temperature, metal)	Stable at elevated temperatures and in contact with aluminum and iron metals. Unstable on contact with metal ions.		

End-Use Product—SYNA16003 Herbicide

Property	Result
Colour	Red-brown
Odour	Oily
Physical state	Liquid
Formulation type	SN (solution)
Guarantee	Bicyclopyrone 200 g/L
Container material and description	HDPE and PET containers, 1 L to 1050 L and bulk
Density	1.079 g/cm^3
pH of 1% dispersion in water	6.8
Oxidizing or reducing action	Not an oxidizing substance, incompatible with strong oxidizers
Storage stability	Physically and chemically stable on storage for one year
Corrosion characteristics	Not corrosive to container materials
Explodability	Not explosive

End-Use Product—Acuron Herbicide

Property	Result
Colour	Olive green to tan
Odour	Paint-like
Physical state	Opaque liquid
Formulation type	SU (suspension)
Guarantee	Bicyclopyrone 7.1 g/L Mesotrione 28.5 g/L Atrazine 120 g/L S-Metolachlor (and R-enantiomer) 257 g/L
Container material and description	Fluorinated and non-fluorinated HDPE
Density	1.099 g/cm^3
pH of 1% dispersion in water	5.0
Oxidizing or reducing action	Not an oxidizing substance, incompatible with strong oxidizers
Storage stability	Physically and chemically stable on storage for one year
Corrosion characteristics	Not corrosive to container materials
Explodability	Not explosive

1.3 Directions for Use

1.3.1 SYNA16003 Herbicide

SYNA16003 Herbicide, containing bicyclopyrone at 200 g/L, is a selective pre-emergent or post-emergent herbicide that will provide short-season residual control of select annual broadleaf weeds plus suppression of proso millet in corn (field, seed and sweet) grown in eastern Canada (Table 1.3.1.1). SYNA16003 Herbicide may be applied once per year at a rate of 37.5 to 50 g a.i./ha (equivalent to 188 to 250 mL/ha, respectively) with ground application equipment only. SYNA16003 Herbicide is to be applied before the emergence of the target weed species.

Table 1.3.1.1 Weed claims for SYNA16003 Herbicide (when applied pre-emergent or post-emergent in corn)

Grassy Weeds	Broadleaf Weeds
37.5 – 50 g a.i./ha: Early-season suppression of proso millet.	37.5 g a.i./ha: Short-season residual control of velvetleaf and eastern black nightshade. 50 g a.i./ha: Short-season residual control of above noted broadleaf weeds plus common ragweed, redroot pigweed and lamb's-quarters. Both rates will also control triazine-resistant and Group 2 Resistant weed biotypes.

1.3.2 Acuron Herbicide

Acuron Herbicide, containing bicyclopyrone at 7.1 g/L of product, mesotrione at 28.5 g/L of product, atrazine at 120 g/L of product and s-metolachlor at 257 g/L of product, is a selective pre-emergent or post-emergent herbicide that will provide season-long residual control of all weeds listed on the current Lumax-brand labels, in addition to short-season residual suppression of proso millet throughout the critical establishment phase of development for corn (field, seed and sweet) grown in eastern Canada (Table 1.3.2.1). Acuron Herbicide may be applied once per year at a rate of 2025 g a.i./ha (equivalent to 4.91 L/ha) with ground application equipment only. Acuron Herbicide is to be applied pre- and post-emergent to broadleaf weeds and pre-emergent to 2 leaf stage for grass weeds except proso millet (pre-emergent only).

Table 1.3.2.1 Weed claims for Acuron Herbicide (when applied pre-emergent or post-emergent in corn)

Grassy Weeds	Broadleaf Weeds
2025 g a.i./ha: Season-long control of barnyard grass, crabgrass (smooth and hairy), fall panicum, foxtail (green, yellow and giant) and witchgrass. Early season suppression of proso millet.	2025 g a.i./ha: Season-long control of nightshade (American, eastern black), common ragweed, lady's-thumb, lamb's-quarters, redroot pigweed, velvetleaf, wild buckwheat and wild mustard Triazine-resistant and Group 2 Resistant weed biotypes will also be controlled.

1.4 Mode of Action

Bicyclopyrone is an inhibitor of 4-hydroxy-phenylpyruvate dioxygenase (HPPD; triketone subclass) and is classified as a Group 27 Herbicide by the Weed Science Society of America (WSSA) and as a Group F2 Herbicide by the HRAC. Bicyclopyrone acts in susceptible plants by ultimately inhibiting the biosynthesis of carotenoids. In the bicyclopyrone-induced absence of carotenoids, the newly forming photosynthetic apparatus is no longer protected from photo-damage and, under illumination, the chlorophyll in the leaf tissue is quickly destroyed. The mode of action of bicyclopyrone is shared with several other commercial herbicide active substances, namely mesotrione, isoxaflutole, topramezone, tembotrione and pyrasulfatole.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The methods provided for the analysis of the active ingredient(s) in the formulations have been validated and assessed to be acceptable for use as enforcement analytical methods.

2.3 Methods for Residue Analysis

High-performance liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media. Methods for residue analysis are summarized in Appendix I, Table 1.

A common moiety method was developed and proposed for data gathering and enforcement purposes for plant and animal matrices. HPLC-MS/MS Methods GRM030.05A in plant matrices and GRM030.08A in animal matrices convert bicyclopyrone and its structurally related metabolites to the common moieties SYN503780 and CSCD686480, which are then expressed as bicyclopyrone equivalents and CSAA915194 equivalents, respectively. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in plant and animal matrices. The proposed enforcement methods were successfully validated in plant and animal matrices by an independent laboratory. Adequate extraction efficiencies were demonstrated using radiolabelled samples of maize forage and grain for plant matrices, and goat liver and hen egg yolk in animal matrices analyzed with the enforcement methods. These methods were later revised as GRM030.05B and GRM030.08B to express both common moieties SYN503780 and CSCD686480 as bicyclopyrone equivalents, to be in line with the residue definitions for plant and animal matrices.

In addition, analyte-specific HPLC-MS/MS method GRM 030.03A was used as a data gathering method in the plant storage stability studies, as it determined residues of bicyclopyrone and SYN503780. HPLC-MS/MS analyte-specific method POPIT MET.116.Rev02 and HPLC-MS/MS common moiety method POPIT MET.117.Rev02 were also used as data gathering methods in the sugarcane processing study from Brazil. Acceptable recoveries (70–120%) were obtained in the stored and processed matrices.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Bicyclopyrone is an inhibitor of the 4-hydroxy-phenylpyruvate dioxygenase (HPPD), and is a member of the triketone family of herbicides. This enzyme is important in the metabolism of the amino acid, tyrosine. Prolonged inhibition of this enzyme results in an increase in plasma tyrosine levels (tyrosinaemia). Excess tyrosine in the blood is metabolized to phenolic acids and excreted in the urine. Following inhibition of HPPD, the maximal extent of the tyrosinaemia is controlled by another catabolic enzyme, tyrosine aminotransferase (TAT). A direct correlation has been shown between tyrosinaemia and ocular toxicity. Published literature indicates that tyrosine accumulates in the anterior aqueous humor, and tyrosine crystals are then deposited in the cornea. It has been demonstrated that the threshold plasma tyrosine concentration for ocular effects in all species is ~1000 nmol/mL, which must be exceeded for a prolonged period of time before ocular lesions develop. It has been concluded that the findings and effect levels for eye lesions established in mice are more relevant than rats for the human risk assessment, since TAT and the resulting plasma tyrosine concentrations are similar between mice and humans. As a result, effects observed on eyes in the rat studies are not quantitatively relevant to humans, as rats are more sensitive to the effects of HPPD inhibitors.

A detailed review of the toxicological database for bicyclopyrone was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to bicyclopyrone.

In acute toxicity testing in rats, bicyclopyrone was of low toxicity via the oral, dermal and inhalation routes. Bicyclopyrone was non-irritating to the skin and minimally irritating to the eyes of rabbits. A modified local lymph node assay conducted in mice to assess the dermal sensitization potential of bicyclopyrone yielded negative results.

In acute toxicity testing in rats SYNA16003 Herbicide was of low toxicity via the oral, dermal and inhalation routes. In rabbits, it was minimally irritating to the eyes and non-irritating to the skin. SYNA16003 was a dermal sensitizer based on the results of a Buehler sensitization study in the guinea pig.

Acuron Herbicide was of slight acute toxicity via the oral route and of low acute toxicity via the dermal and inhalation routes in rats. In rabbits, it was minimally irritating to the eyes and moderately irritating to the skin. Acuron Herbicide was a dermal sensitizer based on the results of a Buehler sensitization study in the guinea pig.

The absorption, distribution, metabolism and excretion of radiolabeled pyridinyl-3-^{14}C bicyclopyrone were investigated in rats at two different doses and in single and repeat studies. Overall, there were similarities between single and repeat dosing, dose level and sex, although males metabolized a higher proportion of parent compound than females. Approximately 95% of the administered dose (AD) was recovered after 24 hours. Absorption was rapid following administration with the maximum concentration of radioactivity detected in plasma within three hours. Elimination of administered radioactivity occurred primarily via urine, followed by feces and bile. There were no radioactive residues in expired air. The highest levels of radioactivity were found in the liver (4% and 3% AD in males and females respectively) and kidney (0.3 % of the AD).

Bicyclopyrone was not extensively metabolized; unchanged parent was the principle radiolabelled component in all dose groups and was primarily excreted via urine. The majority of the metabolites were created via hydroxylation and O-demethylation reactions. Minor metabolites involved glycine conjugation and cleavage between the pyridinyl and bicyclic rings.

Repeat-dose oral toxicity studies were conducted with bicyclopyrone in mice and rats via diet, and in dogs via capsule. Effects in the mouse were limited to increased liver weight and minimal centrilobular hepatocyte hypertrophy. The eye and kidney were the main targets of bicyclopyrone toxicity in the rat. The effects on the eyes included increased corneal opacity and keratitis resulting from tyrosinaemia caused by bicyclopyrone. In the dog, effects were seen on the liver, including increased sciatic nerve degeneration, with some evidence of effects on select neurons. Decreased body weight and body weight gain (bwg) were also observed in the rat and dog. An increase in tyrosine was seen in the rat and the dog.

In a 28-day dermal toxicity study in the rat, corneal degeneration and increased absolute liver and kidney weights were observed. There was no indication of dermal irritation.

Bicyclopyrone was tested for potential genotoxic activity in a battery of in vitro and in vivo assays. Based on the negative results of these studies, bicyclopyrone was not considered genotoxic.

Bicyclopyrone was administered in the diet of mice and rats in long-term studies. In the mouse study, an increased incidence of bronchio-alveolar carcinomas and adenomas was observed at the limit dose only. Concern was tempered by the low concurrent control incidence relative to the historical control data, and the fact that the high dose incidence was within the historical control data range; the lack of statistical significance; and the lack of genotoxicity. Decreased body weight and bodyweight gain were also observed in the study. In the rat study, animals at all doses exhibited an increased incidence of thyroid follicular hypertrophy and chronic progressive nephropathy in the kidney. At the high dose, decreased uterine weights were observed, as well as decreased heart weight (males only). At the mid- and high-dose, eye effects (increased incidence of opaque eyes, corneal damage, eye keratitis and incidence of regenerative corneal hyperplasia) and increased kidney weight were observed. Also, at the mid- and high-dose, eye tumours (squamous cell carcinomas and papillomas) were observed in males, which exceeded the historical control data range. However, the mode of action of HPPD inhibitors has been well documented (REG2005-02, *Mesotrione: Callisto 480 SC Herbicide*) and establishes that rats are far more sensitive to tyrosinaemia than humans. Therefore, the findings of the ocular tumours are considered to be a threshold effect that is qualitatively but not quantitatively relevant to humans.

In a two-generation reproductive toxicity study, rats were exposed to bicyclopyrone via the diet. Reproductive and offspring toxicity occurred in the presence of parental toxicity. Parental toxicity included opacity and roughness of the cornea, as well as kidney pelvic dilation at all doses and decreased bodyweight, bodyweight gain and food consumption at the higher doses. Reproductive effects were seen at the high-dose and included decreased precoital interval, decreased sperm velocities (actual path, straight line) and an increased incidence of abnormal sperm. Offspring toxicity included decreased bodyweight, bodyweight gain and corneal opacity, roughness and vascular keratitis. At the high-dose there was a delay of preputial separation.

In a gavage developmental toxicity study in rats, no adverse effects were seen in the dams at the limit dose. There were fetal skeletal variations (increased incidence of malpositioned pelvic girdle, full or rudimentary supernumary ribs, long costal cartilage and non-ossified cervical vertebra) down to the lowest dose tested. At the mid-dose, there was a decrease in fetal weights and increased supernumerary costal cartilage, while at the high-dose, an increased incidence of sternebrae offset ossification sites and bipartite ossification, as well as asymmetrically aligned costal cartilage at the sternum, was observed. Results indicate the young were more sensitive than adults.

Three gavage developmental toxicity studies were performed, using New Zealand White (NZW) rabbits and two with Himalayan rabbits. In NZW rabbits, an increase in mortality/morbundity and decreased food consumption and body weight gain were observed in high-dose dams.

Treatment at all doses resulted in an increased incidence of a full 13th rib and 27th presacral vertebrae in the fetuses. In the first study conducted on Himalayan rabbits, the dams exhibited macroscopic findings of the stomach wall and an increased incidence of post implantation loss at the high-dose. The fetuses at all doses exhibited an increased incidence of interventricular septum variations, unilateral missing kidney and ureter, and an abnormal heart perimembraneous region. In the mid- and high-dose groups, skeletal variations (increased incidence of malpositioned pelvic girdle, 27 pre-sacral vertebra, supernumerary ribs, and costal cartilage changes) were observed, with an increased incidence of cervical vertebral ossification changes and decreased mean litter weight at the high dose. In the second Himalayan rabbit study, decreased bodyweight gain and increased post-implantation loss were noted in the dams at the high-dose. Mortality was also observed. In mid and high-dose fetuses, skeletal variations (increased incidence of full supernumerary thoracolumbar ribs and slowed costal cartilage development) were observed. At the high-dose, there was decreased fetal weight, increased incidences of cleft jaw/palate, heart abnormalities, uterine horn absent/threadlike or ovary misshapen, as well as increased incidences of malpositioned oesophagus, cervical vertebral irregularities, rib/costal cartilage abnormalities (fused/interrupted/short) and skeletal variations (cervical vertebrae structural variations, cervical vertebrae ossification irregularities, and caudal displacement of pelvic girdle). Additionally, there was an increase in the incidence of incompletely ossified pubis and of missing ureter and kidney. As fetal malformations were noted in the absence of maternal toxicity in the two Himalayan rabbit studies, both studies were considered as co-critical and the lower developmental no observed adverse effect level (NOAEL) of the two studies was selected as the most appropriate for assessing the developmental toxicity in the rabbit.

Functional observational batteries for neurotoxicity in repeat-dose dietary rat toxicity studies were negative. In a gavage acute neurotoxicity study in rats, decreased ambulatory motor activity and mean ambulatory counts were observed, but only on the day of dosing. There was no evidence of neurotoxicity in the rat 90-day repeat dose dietary neurotoxicity study. There was a slight increase in the incidence sciatic nerve degeneration and of chromatolysis/swelling of select neurons in the dorsal root ganglia of dogs exposed to bicyclopyrone for an extended period of time. The weight of evidence suggests bicyclopyrone is not neurotoxic.

Bicyclopyrone did not adversely impact the immune system as measured by the antibody plaque forming cell assay. There was no indication in the broader toxicology database that the immune system was adversely affected by bicyclopyrone.

Results of the toxicology studies conducted on laboratory animals with bicyclopyrone and its associated end-use products are summarized in Tables 2 and 3 of Appendix I. The toxicology endpoints for use in the human health risk assessment are summarized in Table 4 of Appendix I.

Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents to the PMRA that include adverse effect to Canadian health or the environment. Bicyclopyrone is a new active ingredient pending registration for use in Canada and elsewhere. As a result, there are no incident reports for this active ingredient in the PMRA database.

3.1.1 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for bicyclopyrone. The database contains the full complement of required studies including a developmental toxicity study in rats, three developmental studies in rabbits (2 Himalayan, 1 NZW) and a reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, no evidence of sensitivity of the young was observed in the 2-generation rat reproductive toxicity study. However, in the developmental toxicity study in rats, skeletal malformations were observed in fetuses at a dose that produced no effects in the dams. In the NZW rabbit developmental toxicity study, skeletal variations were observed at a dose that produced mortality, decreased food consumption, bodyweight gain and bodyweight loss in the dams. However, in the Himalayan rabbit developmental toxicity studies, skeletal variations, heart effects and an increased incidence of unilateral missing kidney and ureter (a malformation) were observed in the absence of maternal toxicity, thus indicating fetal sensitivity.

Overall, the database is adequate for determining the sensitivity of the young and effects on the young are well characterized. The malformations in rabbits were considered serious endpoints and occurred in the absence of maternal toxicity. Therefore, the *Pest Control Products Act* factor was retained at 10-fold when using the rabbit developmental toxicity study to establish the point of departure for risk assessment. For all other exposure scenarios the *Pest Control Products Act* factor was reduced to 1-fold.

3.2 Acute Reference Dose

Females 13-49 Years of Age

To estimate acute dietary risk (1 day), the Himalayan rabbit developmental toxicity studies were considered to be co-critical for risk assessment. The overall NOAEL was 1 mg/kg bw/day, based on missing kidneys and ureters at the lowest observed adverse effect level (LOAEL) of 10 mg/kg bw/day. This effect is relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was retained at 10-fold.

The composite assessment factor (CAF) is thus 1000.

The ARfD was calculated according to the following formula:

$$\text{ARfD (females 13-49 years of age)} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{1 \text{ mg/kg bw}}{1000} = 0.001 \text{ mg/kg bw of bicyclopyrone}$$

General Population (excluding females 13-49 years of age)

To estimate acute dietary risk (1 day), the acute neurotoxicity study with a NOAEL of 200 mg/kg bw was selected for risk assessment. At the LOAEL of 2000 mg/kg bw, decreased motor activity and mean ambulatory counts were observed. These effects resulted from a single exposure and are therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold.

The CAF is thus 100.

The ARfD was calculated according to the following formula:

$$\text{ARfD (gen. pop.)} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{200 \text{ mg/kg bw}}{100} = 2 \text{ mg/kg bw of bicyclopyrone}$$

3.3 Acceptable Daily Intake

To estimate risk from repeat dietary exposure, the long-term rat dietary study with a LOAEL of 0.28 mg/kg bw/day was selected for risk assessment. At the LOAEL, thyroid and kidney effects were observed. This study was considered the most appropriate in the database relevant to this duration. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. An additional uncertainty factor of 3-fold was applied for the lack of a NOAEL. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold.

The CAF is thus 300.

The acceptable daily intake (ADI) was calculated according to the following formula:

$$\text{ADI bicyclopyrone} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{0.28 \text{ mg/kg bw/day}}{300} = 0.001 \text{ mg/kg bw/day of bicyclopyrone}$$

The ADI provides a margin of 1000 to the NOAEL for malformations in the developmental toxicity studies in the rabbit.

Cancer Assessment

Tumours (bronchio-alveolar adenomas and carcinomas) in the 80 week mouse study were observed in the high-dose males at 1027 mg/kg bw/day and could not be ruled out as being treatment related. However, there is a large margin between the dose at which treatment related tumours were observed (1027000) and the ADI. A threshold approach was considered to be appropriate. It was determined that the eye tumours (squamous cell carcinomas and papillomas in males) in the rat study were qualitatively but not quantitatively relevant to humans, based on the mode of action for HPPD inhibitors. A threshold approach was considered appropriate for these tumours, with the margin of 284000 between the dose at which tumours were observed to the ADI.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Short- and Intermediate-term Dermal and Inhalation Exposure

For short- and intermediate-term occupational exposures via the dermal and inhalation routes, the Himalayan rabbit developmental toxicity studies were considered to be co-critical for risk assessment. The overall NOAEL was 1 mg/kg bw/day, based on the malformation of missing kidney and ureter at the LOAEL of 10 mg/kg bw/day. The available 28-day dermal study did not assess the relevant endpoints of concern. A short-term inhalation study was not available.

The target margin of exposure (MOE) for these scenarios is 1000, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability as well as a factor of 10-fold for the reasons outlined in the *Pest Control Products Act* Hazard Characterization section. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Occupational exposures to SYNA16003 Herbicide and Acuron Herbicide are characterized as short-term duration and mainly via the dermal and inhalation routes for mixer/loader and applicator, and through the dermal route for post-application re-entry workers.

3.4.1.1 Dermal Absorption

The applicant submitted rat and human in vitro studies, and a rat in vivo dermal absorption study. Each study was of good quality. All studies were conducted with comparable application rates of the same formulation, but the in vitro studies were conducted for an exposure duration of 24 hours; whereas, the in vivo study exposure duration was 6 hours. Therefore, these studies do not meet the NAFTA "triple pack" approach. However, the rat in vivo study was chosen to determine a dermal absorption value.

The rat in vivo dermal absorption study was conducted using a 20% suspension formulation containing ^{14}C-labelled bicyclopyrone representing undiluted SYNA16003 (2400 µg/cm^2), and two dilutions, 20 µg/cm^2 and 5 µg/cm^2, proposed to represent typical use in the field. Following an exposure period of six hours, application site skin areas were washed to remove the non-absorbed dose. Groups of rats were also monitored up to 24, 72, and 120 hours after application, to assess the fate of skin-bound residues. At the termination of the monitoring periods, the potentially absorbed dose was calculated by summing residues in urine, feces, cage wash, treated skin including tape strips (skin-bound residue), untreated skin, blood and carcass (including organs) from each rat.

Most total residue recoveries were greater than 100% which hindered the determination of the fate of residues. Further to this, the exposure duration was less than the recommended 10 hours for an agricultural worker. Nonetheless, an estimate of dermal absorption was determined based on the low dose, as dermal absorption was greatest at this dose. Absorption at the 5 µg/cm^2 dose suggests that bicyclopyrone continues to be absorbed from the skin into the body beyond the exposure period.

The dermal absorption value of 22% was determined from the six-hour exposure of rats to the lowest application rate of 5µg/cm^2, and sacrificed after 120 hours. This value is not expected to underestimate dermal absorption, based on the likelihood of an agricultural workday of 8 to 10 hours, and is considered to be conservative since some residue was retained in the skin and not all of the residue will become systemically available. The dermal absorption value of 22% was concluded to be appropriate for risk assessments of SYNA16003 Herbicide and Acuron Herbicide formulations.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/Loader/Applicator Exposure and Risk Assessment

Individuals have potential for exposures to SYNA16003 Herbicide and Acuron Herbicide during mixing, loading and application. Dermal and inhalation exposure estimates for farmers and custom applicators were generated from the Pesticide Handlers Exposure Database (PHED).

Exposures to farmers and custom applicators mixing, loading and applying SYNA16003 Herbicide and Acuron Herbicide are expected to be short-term in duration and to occur primarily by the dermal and inhalation routes. Exposures were estimated using a closed mix/load scenario for mixers and loaders of SYNA16003 Herbicide, and using an open-pour scenario for mixers and loaders of Acuron Herbicide. Exposures were estimated when applying SYNA16003 Herbicide and Acuron Herbicide to corn using open-cab ground boom equipment.

The exposure estimates are based on mixers and loaders of SYNA16003 Herbicide wearing a long-sleeved shirt and long pants, chemical-resistant gloves, socks, shoes and eye protection. During application, workers must wear coveralls over a long-sleeved shirt and long pants, socks and shoes. The exposure estimates are based on mixers, loaders, and applicators of Acuron Herbicide wearing coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, and shoes with socks. However, chemical-resistant gloves are not required during application of Acuron Herbicide. The custom applicator area of corn treated per day of 140 ha/day is expected to address the corn area treated by a farmer of 107 ha/day when treating with the same mixing, loading, and application equipment.

Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted.

Dermal exposures were estimated by coupling the unit exposure values with the application rate, area treated per day, and the dermal absorption value. Inhalation exposures were estimated by coupling the unit exposure values with the application rate, area treated per day, and 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult bw.

Exposure estimates were compared to the toxicological endpoints (NOAELs) to obtain the MOE.

Table 3.4.2.1 Risk Estimates for Mixing/Loading/Applying Products Containing Bicyclopyrone

Scenario	Maximum Application Rate (kg a.i./ha)	Area Treated Per Day[1] (ha/day)	PHED[2] Mixer/Loader Unit Exposure (µg/kg a.i.)		PHED[2] Applicator Unit Exposure (µg/kg a.i.)		M/L/A Exposure[3] (mg/kg bw/day)		Combined MOE[4]
			Der-mal	Inhalation	Der-mal	Inhalation	Der-mal	Inhalation	
SYNA16003 Herbicide									
Farmer and Custom	0.05	140	18.95	0.11	21.04	0.96	7.70E-04	9.36E-05	1158
Acuron Herbicide									
Farmer and Custom	0.035	140	32.77	1.6	21.04	0.96	7.25E-04	1.57E-04	1134

1 Refined corn area treated per day value (Syngenta, 2012).

2 Canadian PHED Tables version 1.1 (2002).

3 Exposure (mg/kg bw/day) = AR * UE * ATPD * A * CF / BW.

AR = application rate (kg a.i./ha); maximum application rate.

UE = unit-exposure (µg a.i./kg a.i. handled), PHED version 1.1 scenario database for dermal and inhalation routes, and PPE.

ATPD = area treated per day (ha).

A = dermal absorption = 22% (as a proportion = 0.22); inhalation systemic absorption, considered to be 100% = 1.

CF = conversion factor (0.001 mg/µg).

BW = bodyweight, for an adult is 80kg.

4 Margin of Exposure (MOE) = NOAEL / Exposure [$(M/L/A)_{dermal}$ + $(M/L/A)_{inhalation}$]

Target MOE = 1000.

NOAEL = dermal and inhalation occupational NOAEL of 1 mg/kg bw/day for short- to intermediate-term durations.

Exposure = dermal and inhalation estimates.

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

There is potential for exposures of workers re-entering areas treated with SYNA16003 Herbicide and Acuron Herbicide performing scouting and hand-setting irrigation equipment. The duration of exposure is considered to be short-term, and the primary route of exposure for workers re-entering treated areas would be through the dermal route.

Chemical-specific dislodgeable foliar residue (DFR) data were not submitted. Dermal exposure to workers entering treated areas is estimated by coupling default DFR values (25% DFR on the day of application and 10% dissipation per day), with activity-specific transfer coefficients (PMRA 2012 ARTF Agricultural Transfer Coefficients).

The vapour pressure of bicyclopyrone is $< 5 \times 10^{-6}$ Pa (5×10^{-9} kPa) at 25°C, which is lower than the NAFTA inhalation study waiver of $< 1 \times 10^{-4}$ kPa at 20-30°C for outdoor use. Therefore, no post-application inhalation assessment is required.

Exposure estimates were compared to the toxicological endpoint to obtain the MOE.

Table 3.4.2.2 Risk Estimates for Workers Re-entering Field Corn Treated with SYNA16003 Herbicide or Acuron Herbicide Containing Bicyclopyrone

Re-entry Scenario	TC [1] (cm^2/h)	DFR [2] ($\mu g/cm^2$) on Day of Application	Daily Exposure[3] (mg/kg bw/day)	MOE [4]	Re-entry Interval (days)
SYNA16003 Herbicide					
hand set irrigation	1750	0.125	0.004813	208	15
Scouting, minimum foliage, low height	210		0.000578	1732	0
Acuron Herbicide					
hand set irrigation	1750	0.0875	0.00337	297	12
Scouting, minimum foliage, low height	210		0.000404	2474	0

PMRA Transfer Coefficients memo (PMRA 2012); Field corn scouting, minimum foliage and low height.

Based on DFR on the day of application = Application rate of SYNA16003 (0.50μg/cm2) or Acuron (0.35μg/cm2) × amount retained on foliage (25%).

Daily exposure (dermal) = DFR × TC × ET × DA × CF / BW.

ET = 8 hr workday, DA = 22%, CF = 0.001mg/μg, and BW = 80 kg bw.

MOE = NOAEL (mg/kg bw/day)/Daily Exposure (mg a.i./kg bw/day); NOAEL of 1 mg/kg bw/day (short to intermediate duration); target MOE = 1000.

3.4.3 Residential Exposure and Risk Assessment

These end-use products do not contain residential uses.

3.4.3.1 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal. Application is limited to agricultural crops only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools and recreational areas. This takes into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in plant products and animal commodities is: bicyclopyrone and its structurally related metabolites determined as the common moieties SYN503780 and CSCD686480, expressed as bicyclopyrone equivalents. The enforcement analytical methods are valid for the quantitation of SYN503780 and CSCD686480 residues in crop and livestock matrices.

The residues of bicyclopyrone and the metabolite SYN503780 are stable in representative raw agricultural commodity (RAC) matrices from five crop categories (high water, high oil, high protein, high starch and high acid content) for up to 24 months when stored at ≤-20°C. The residues of bicyclopyrone, SYN503780 and CSCD686480 are stable in bovine tissues, milk and eggs for up to 16 months when stored in a freezer at ≤-10°C.

Due to the lack of detectable residues of SYN503780 and CSCD686480 in sugarcane stalks (RAC), no processing into sugar, molasses or bagasse was performed. No detectable residues of SYN503780 and CSCD686480 were found in the raw agricultural commodities of field corn and the processed commodities of aspirated grain fractions, flour, germ, meal, hulls, oil, grits, gluten and starch. An adequate feeding study was carried out to assess the anticipated residues in cattle matrices resulting from the current uses. Crop field trials conducted throughout the United States for corn (field, pop and sweet) and Australia for sugarcane using end-use products containing bicyclopyrone at approved rates are sufficient to support the proposed maximum residue limits (MRLs).

3.5.2 Drinking Water

The following sections review the estimated environmental concentrations (EECs) of bicyclopyrone resulting from water modelling. For the drinking water modelling, the parent bicyclopyrone alone was modelled as the major environmental transformation products (SYN503780 and CSCD656832) that could potentially reach surface and groundwater do not contain the moiety of concern and thus, were not included in the residue definition for drinking water.

3.5.2.1 Application Information and Model Inputs

Bicyclopyrone is an herbicide proposed for use on corn in Eastern Canada only. The maximum annual application rate is a single application of 50 g a.i./ha. Application information and the main environmental fate characteristics used in the models are summarized below.

Table 3.5.2.1 Major groundwater and surface water model inputs for Level 1 and Level 2 (groundwater only) assessment of bicyclopyrone

Type of Input	Parameter	Value
Application Information	Crops to be treated	Corn
	Maximum allowable application rate per year (g a.i./ha)	50
	Maximum rate each application (g a.i./ha)	50
	Maximum number of applications per year	1
	Minimum interval between applications (days)	n/a
	Method of application	Fieldsprayer, on the soil surface or on foliage
Environmental Fate Characteristics	Hydrolysis half-life at pH 7 (days)	Stable
	Photolysis half-life in water (days)	50
	Adsorption K_{OC} (mL/g)	11.2 (20th percentile of 17 K_{OC} values for parent)
	Aerobic soil biotransformation half-life (days)	177 (90th percentile confidence bound on mean of 14 half-life values adjusted to 25°C)
	Aerobic aquatic biotransformation half-life (days)	stable
	Anaerobic aquatic biotransformation half-life (days)	8874 (80th percentile of four half-life values)

3.5.2.2 Estimated Concentrations in Drinking Water Sources: Level 1 Modelling

Estimated environmental concentrations (EECs) of bicyclopyrone in potential drinking water sources (groundwater and surface water) were generated using computer simulation models. An overview of how the EECs are estimated is provided in the PMRA's Science Policy Notice SPN2004-01, *Estimating the Water Component of a Dietary Exposure Assessment*. EECs of bicyclopyrone in groundwater were calculated using the PRZM-GW model to simulate leaching through a layered soil profile over a 50-year period. The concentrations calculated using PRZM-GW are average concentrations in the top 1m of the water table.

EECs of bicyclopyrone in surface water were calculated using the PRZM/EXAMS models, which simulate pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. Pesticide concentrations in surface water were estimated in a vulnerable drinking water source, a small reservoir.

A Level 1 drinking water assessment was conducted using conservative assumptions with respect to environmental fate, application rate and timing, and geographic scenario. The Level 1 EEC estimate is expected to allow for future use expansion into other crops at this application rate across Canada. The table below lists the application information and main environmental fate characteristics used in the simulations.

Ten initial application dates between April and July were modelled. The model was run for 50 years for all scenarios. The largest EECs of all selected runs are reported in the table below.

Table 3.5.2.2.1 Level 1 Estimated Environmental Concentrations of Bicyclopyrone in Potential Drinking Water

Compound	**Groundwater EEC (µg a.i./L)**		**Surface Water EEC (µg a.i./L)**	
			Reservoir	
	Daily[1]	**Yearly[2]**	**Daily[3]**	**Yearly[4]**
Bicyclopyrone (1 × 50 g a.i./ha)				
Maximum across Canada	42	42	3.3	0.73
Maximum in Eastern Canada (ON, QC, Atlantic)	26	24	3.3	0.73

Notes:

[1] 90th percentile of daily average concentrations.

[2] 90th percentile of 365 day moving average concentrations.

[3] 90th percentile of yearly peak concentrations.

[4] 90th percentile of yearly average concentrations.

Level 2 Modelling

A refined Level 2 assessment was also conducted with Eastern Canada corn scenarios. EECs obtained from this refinement are summarized in the table below.

Table 3.5.2.2.2 Level 2 Estimated Environmental Concentrations of Bicyclopyrone in Potential Drinking Water

Compound	Groundwater EEC (µg a.i./L)	
	Daily[1]	Yearly[2]
Bicyclopyrone (1 × 50 g a.i./ha)		
Maximum in Eastern Canada (ON, QC, Atlantic)	17	17

1 90th percentile of daily average concentrations.

2 90th percentile of 365 day moving average concentrations.

3.5.3 Dietary Risk Assessment

Acute and chronic dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 3.16, 03-08-d). This software uses 2003-2008 food consumption data from the United States Department of Agriculture's National Health and Nutritional Examination Survey, What We Eat in America.

3.5.3.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the refined chronic non-cancer analysis for bicyclopyrone: 100% crop treated, default and experimental processing factors (where available), residues of sweet corn (kernels plus cob with husks removed) (K+CWHR) based on supervised trial median residue values, residue values at limit of quantitation (LOQ) for field corn grain, popcorn grain and sugarcane; and anticipated residues for all livestock commodities. The refined chronic dietary exposure from all supported bicyclopyrone food uses (alone) for the total population, including infants and children, and all representative population subgroups is less than 16% (0.000153 mg/kg bw/day) of the ADI. Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to bicyclopyrone from food and drinking water is 41% (0.000405 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for infants, however, they are not expected to be exposed to greater than 100% of the ADI (0.000998 mg/kg bw/day).

3.5.3.2 Acute Dietary Exposure Results and Characterization

The following assumptions were applied in the refined acute analysis for bicyclopyrone: 100% crop treated, default and experimental processing factors (where available), residues of sweet corn K+CWHR based on maximum residue values, MRL values (at LOQ) for field corn grain, popcorn grain and sugarcane, and anticipated residues for all livestock commodities. The refined acute dietary exposure (food alone) for all supported bicyclopyrone registered commodities is estimated to be 0.01% (0.000145 mg/kg bw) of the ARfD for the general population, and 10% (0.000094 mg/kg bw) of the ARfD for females 13–49 years old (95th percentile, deterministic). Aggregate exposure from food and drinking water is acceptable for the general population at 0.15% of the ARfD (0.003041 mg/kg bw), and for females 13–49 years old at 97% of the ARfD (0.00966 mg/kg bw).

3.5.4 Aggregate Exposure and Risk

As there are no residential uses, the aggregate risk for bicyclopyrone consists of exposure from food and drinking water sources only.

3.5.5 Maximum Residue Limits

Table 3.5.5 Proposed Maximum Residue Limits

Commodity	Recommended MRL (ppm)
Sweet corn K+CWHR	0.03
Field corn grain, popcorn grain, sugarcane cane	0.02
Meat byproducts of cattle, goats, horses and sheep	1.5
Meat byproducts of hogs	0.20
Meat and fat of cattle, goats, horses, hogs, sheep and poultry; meat byproducts of poultry	0.02
Milk and eggs	0.02

MRLs are proposed for each commodity included in the listed crop groupings in accordance with the Residue Chemistry Crop Groups webpage in the Pesticides and Pest Management section of the Health Canada website.

For additional information on MRLs in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in animal and plant matrices, analytical methodologies, field trial data, and acute and chronic dietary risk estimates are summarized in Tables 1, 5 and 6 in Appendix I.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Bicyclopyrone has very high aqueous solubility. Based on its low vapour pressure and Henry's law constant, volatilization of bicyclopyrone from moist soil or water surfaces is unlikely to be a significant route of dissipation in the environment.

In the terrestrial environment, bicyclopyrone undergoes biotransformation resulting in several major and minor transformation products. In laboratory soil studies, bicyclopyrone was transformed primarily by phototransformation and microbial degradation. Additional laboratory studies showed bicyclopyrone is stable to hydrolysis and microbial degradation under anaerobic conditions. Bicyclopyrone is very highly mobile in soil; indicating a potential to leach. Half-lives for phototransformation in soil ranged from 4 to 13 days and resulted in three major transformation products, SYN503780, CSCD656832 and CSCC163768. Bicyclopyrone undergoes microbial degradation in aerobic soil with half-lives ranging from 20 to 350 days and is classified as slightly persistent to persistent, transforming to several transformation products, of which two are considered major, SYN503780 and CSCD656832. SYN503780 and the minor transformation product, CSAA806573 were found to be non-persistent, with corresponding half-lives of <1 day - 5.2 days and <1 days, respectively. Mobility studies for the major soil transformation products indicate that CSCD656832 is expected to be moderately to slightly mobile in soil whereas SYN503780 is expected to be very highly mobile. Under field conditions, bicyclopyrone was non-persistent, with half-lives of 1.7 to 5 days in bareground plot studies conducted at three sites in North America.The fate of the major soil transformation products, SYN503780 and CSCD65832, were also characterized under field conditions. The field dissipation studies showed SYN503780 was non-persistent; it formed and reached its peak concentration at seven days after application before decreasing in a North American terrestrial field dissipation study. CSCD656832 was not detected in the study a field study conducted in a Canadian relevant ecoregion (Iowa), but was reported to reach a maximum of 11.8% of the applied concentration after 21 days and subsequently dissipated to 2.3% (180 days) in a field study conducted in the southern United States (Georgia). Additional prospective groundwater monitoring studies were conducted to characterize the leaching potential of bicyclopyrone and SYN503780 under field conditions. The prospective groundwater monitoring studies showed that the majority of added bicyclopyrone remained in the soil and entered groundwater at the end of the studies. The SYN503780 transformation product was detected in wells at sampling intervals up to three years after application, indicating that it may be more persistent than predicted and has the potential to leach to groundwater.

Bicyclopyrone may move to groundwater via leaching, and may move to surface water bodies via spray drift and runoff of dissolved or sorbed residues. In the aquatic environment, bicyclopyrone is considered stable to hydrolysis at environmentally relevant pH values and therefore, hydrolysis is not expected to be a significant route of transformation in most water bodies. Bicyclopyrone photodegrades slowly in water, with respective half-lives of 11 and 50 days at pH 5 and 7, and 74.8 days in natural water to the major transformation products, CSAA589691 and CSCC163768, and two minor transformation products. Photolysis is not expected to be a significant aquatic transformation pathway. Bicyclopyrone is stable in anaerobic aquatic systems, and only degrades very slowly in aerobic aquatic systems, with half-lives of 393-681 days (mean of 550; n=4). As bicyclopyrone is persistent in aerobic and anaerobic aquatic systems, prolonged exposure of aquatic organisms to bicyclopyrone may occur under the proposed use pattern.

Bicyclopyrone is not expected to bioaccumulate in biota, as the log K_{OW} value is equal to or less than 0.25 at environmentally relevant pH values. Data related to the environmental fate of bicyclopyrone and its major transformation products are found in Appendix 1, Table 7 and Table 8. The transformation pathways for bicyclopyrone in aerobic soil and in water are summarized in Figure 2 of Appendix 1.

Overall, the primary routes of dissipation in the terrestrial environment are phototransformation and microbially mediated degradation in aerobic soils (Figure 1). Although bicyclopyrone and its transformation products are not expected to persist in soils, they may leach to groundwater and persist for several years. In the aquatic environment, the main route of dissipation is expected to be photolysis in shallow, clear waters (Figure 2) and slow biotransformation in other aquatic systems. Bicyclopyrone residues are not expected in the atmosphere, and long range atmospheric transport is not expected.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the RQ is then compared to the level of concern (LOC = 1 for most species, 0.4 for pollinators and 2 for beneficial arthropods [predatory mite and parasitoid wasp]). If the screening level RQ is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level RQ is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

As multiple ER_{50} values were available for terrestrial vascular plants, the program ETX 2.0 was used to generate a species sensitivity distribution (SSD) based on normally distributed toxicity data. The hazardous rate to 5% of the species (HR_5) was then calculated for vegetative vigour from the SSD. The HR_5 is the rate which is theoretically protective for 95% of species. At the HR_5 exposure level, 5% of all species will be exposed to a rate which exceeds their LR_{50} toxicity value. The variability around the fraction of species affected value is indicated by the lower and upper confidence limits, which indicates the minimum and maximum percent of species that may be affected at the HR_5 value. The HR_5 values were used to calculate the RQ for terrestrial vascular plants instead of the most sensitive species tested. This provides a more scientifically robust endpoint, which uses all of the data.

The use pattern does not involve an expansion on corn nor does it involve an increase in the application rate over those already registered for mesotrione, S-metolachlor and R-enantiomer, and atrazine. Therefore, no increased risk to the environment is expected and an environmental risk assessment was not required for these three co-actives.

4.2.1 Risks to Terrestrial Organisms

A risk assessment of bicyclopyrone was conducted for terrestrial organisms. For acute toxicity studies, uncertainty factors of 1/2 and 1/10 the EC_{50} (LC_{50}) are typically used in modifying the toxicity values for terrestrial invertebrates, birds and mammals when calculating RQs. No uncertainty factors are applied to chronic NOEC endpoints.

A summary of the toxicity data of bicyclopyrone to non-target organisms is presented in Table 9 while the screening level risk assessment of bicyclopyrone to non-target organisms except for birds and small wild mammals is presented in Table 10.

Earthworms: Bicyclopyrone and an end-use formulation of bicyclopyrone, A16003E (containing 197 g bicyclopyrone/L), were not acutely toxic to earthworms up to the highest concentration tested. The screening level risk assessment was determined by comparing this value to the EECs for the highest use rate scenario of bicyclopyrone on corn (50 g a.i./ha). The LOC was not exceeded for earthworms.

Bees (pollinators): The effect of bicyclopyrone and a bicyclopyrone formulated product, A16003E (containing 197 g bicyclopyrone/L), were observed on honeybees on an acute oral and contact basis. No treatment related mortality of honey bees were observed in the acute oral and contact exposure of bicyclopyrone. Exposure of bees to A16003E resulted in treatment related mortality only in the highest test concentration in both oral and contact exposure (12 and 32% mortality in the oral and contact exposure, respectively). Sublethal effects to bees were observed upon acute oral and contact exposure to bicyclopyrone and A16003E; several bees exposed to bicyclopyrone on both an oral and contact basis displayed coordination problems soon after study initiation, however, recovery was rapid and no abnormal behaviour was observed in any bees by the 24-hour observation period. Bees showed signs of reduced coordination and delayed reactions to stimuli from both oral and contact exposure to A16003E, however, recovery was apparent in all but the highest test group. Based on mortality, the resulting RQs for both acute oral and contact exposure of bees to bicylclopyrone and A16003E were below the LOC.

Beneficial arthropods: Acute exposure of the bicyclopyrone formulated product, A15749AD, when applied on glass plates, affected the survival but did not affect the fecundity of the parasitic wasp, *Aphidius rhopalosiphi*, and the predatory mite, *Typhlodromus pyri*. The LOC was exceeded (8.3) for the most sensitive species (parasitic wasp) based on the in-field exposure screening level but not for off-field exposure.

A subsequent higher-tiered acute exposure of the parasitic wasp, *Aphidius rhopalosiphi*, to the bicyclopyrone formulated product, A15936Z, on barley seedlings resulted in no statistically significant differences in mortality or fecundity between the treated and control groups. The RQs for the parasitic wasp resulting from exposure to bicyclopyrone did not exceed the LOC at the screening level. Although a higher-tiered study is required for two species, the lack of any adverse effects observed in the parasitic wasp coupled with the low RQs precludes the requirement for additional higher-tiered studies.

Birds: Bicyclopyrone was not toxic to birds on an acute oral or dietary basis. No treatment related dietary effects were observed in the bobwhite quail (*Colinus virginianus*) and mallard duck (*Anas platyrhynchos*), however, mortalities were observed for the bobwhite quail and canary (*Serinus canaria)* under acute oral exposure conditions. The RQ for birds resulting from acute oral or dietary exposure to bicyclopyrone did not exceed the LOC at the screening level. The summary of the screening level risk assessment to birds is presented in Table 11.

Following chronic exposure to bicyclopyrone, reproduction of bobwhite quail and mallard duck were affected at a concentration of less than 200 mg a.i./kg diet (equivalent to less than 19.1 mg a.i./kg bw/day; decrease in mean body weight of hatchlings) and less than 35 mg a.i./kg diet (equivalent to less than 4.3 mg a.i./kg bw/day; decrease in mean body weight of hatchlings), respectively. As this was the lowest test concentration tested, the lowest observable effect level (LOEL) was assessed against the EEC. The screening level reproductive RQ for birds, based on on-field exposure at the maximum residue level, did not exceed the LOC. Table 12 shows the expanded screening level risk assessment which includes all feeding guilds and both on- and off-field exposure scenarios at the maximum residue level. The table shows that in order for the off-field LOC to be exceeded, the LOEL or NOEL used to calculate the estimated dietary exposure (EDE) would need to be several magnitudes higher than the current LOEL. Based on these results, the reproductive risk to birds when bicyclopyrone is applied to corn is anticipated to be low. A new bird reproductive study will not be required at this time.

Mammals: The toxicity of bicyclopyrone to rats was used to determine the risk to small terrestrial mammals. No adverse effects were reported when rats were exposed to bicyclopyrone on an acute basis. The RQ for mammals resulting from acute exposure to bicyclopyrone did not exceed the LOC at the screening level (Table 11).

The multigenerational dietary reproductive exposure of bicyclopyrone to rats resulted in a reduction in the body weight and the reduction in body weight gain of offspring. The NOEL and LOEL were determined to be 1.9 and 38.4 mg/kg bw/d, respectively. The RQ calculated with the NOEL resulting from dietary reproductive exposure marginally exceeded the LOC (RQs of 1.2, 2.4, and 1.3 for small-, medium- and large-sized mammals, respectively) at the screening level (Table 13). The screening level risk assessment was therefore expanded to include all feeding guilds and exposure levels, as well as both on- and off-field exposure scenarios. This is presented in Table 13. Results from this assessment suggest a relatively low likelihood that adverse effects on mammal reproduction would be observed from the use of bicyclopyrone. The RQs only marginally exceed the LOC with maximum residue values for several feeding guilds but were below the LOC when considering mean residue values for all feeding guilds and mammal sizes. Furthermore, when the RQs are calculated using the LOEL, the resulting values (not shown here) are all well below the LOC for both maximum and mean residue values. This indicates that concentrations of bicyclopyrone in the environment following its application would not reach levels at which adverse effects on mammal reproduction was observed under laboratory conditions. Based on the overall results, the risk to small mammals is anticipated to be low.

Non-target plants: The effect of bicyclopyrone to non-target plants was determined through the exposure of the formulated end-use product, A15749F or NOA 449280 EC (containing 150 g a.i./L), through a seedling emergence and vegetative vigour assay using standard crop species. Bicyclopyrone was found to be toxic to non-target plants in seedling emergence and vegetative vigour studies using standard crop species. Using the HR_5 value for formulated end-use product from the SSD of ER_{50} values for vegetative vigour, the calculated RQ exceeded the LOC at the screening level.

The risk to terrestrial non-target plants was further characterized by looking at off-field exposure from drift. Based on the RQs calculated using the off-field EECs from drift, the LOC (RQ = 3.8) for non-target terrestrial plants was still exceeded for vegetative vigour. Spray buffer zones will be required on product labels to protect terrestrial non-target plants.

4.2.2 Risks to Aquatic Organisms

A risk assessment of bicyclopyrone, two transformation products, CSAA589691 and CSCC163768, and one formulated product, A16003E (containing 197 g bicyclopyrone/L), was conducted for freshwater and marine aquatic organisms based on available toxicity data. For the assessment of risk, toxicity endpoints from the most sensitive species was used as surrogates for the wide range of species that can be potentially exposed following treatment with bicyclopyrone.

For acute toxicity studies, uncertainty factors of 1/2 and 1/10 the EC_{50} (LC_{50}) are typically used for aquatic plants and invertebrates, and fish species, respectively, when calculating RQs. No uncertainty factors are applied to chronic no observed effect concentration (NOEC) endpoints. For groups where the LOC is exceeded (in other words, RQ ≥ 1), a refined Tier 1 assessment is conducted to determine risk resulting from spray drift and runoff separately. RQs for bicyclopyrone and its transformation products were calculated based on the highest maximum seasonal application rate for all uses. The screening level RQs for bicyclopyrone and its transformation products are summarized in Table 10.

A summary of the toxicity data to non-target organisms is presented in Table 9.

Freshwater invertebrates: No adverse effects were observed when daphnids were exposed to bicyclopyrone and A16003E on an acute and chronic basis. The acute and chronic RQs for daphnids did not exceed the LOC at the screening level.

Freshwater fish and amphibians: The toxicity of bicyclopyrone to two freshwater species of fish was assessed for acute exposure (rainbow trout and fathead minnow) while toxicity from chronic exposure (early life-stage) was assessed on fathead minnow. The acute toxicity of the bicyclopyrone formulated product, A16003E, was also assessed on the rainbow trout. No adverse effects were observed in any of the above mentioned acute or chronic studies to the rainbow trout and fathead minnow.

The risk to aquatic life stages of amphibians was assessed using fish toxicity values as surrogate endpoints. This risk was characterized at the screening level by comparing EECs in 15 cm water depth with amphibian toxicity endpoints for bicyclopyrone.

The screening level RQs for freshwater fish and amphibians for both acute and chronic exposure to bicyclopyrone and its formulated product did not exceed the LOC.

Freshwater algae and vascular plants: Bicyclopyrone was found to inhibit the growth rate and yield of freshwater nonvascular green alga (*Pseudokirchneriella subcapitata*) and freshwater diatom algal species (*Navicula pelliculosa*) on an acute basis but was found not to have any adverse effects to freshwater nonvascular cyanobacterium ("blue-green alga"; *Anabaena flos-aquae*) on an acute basis. The bicyclopyrone formulated product, A16003E or NOA449280 SL (200) (guarantee 197 g NOA 449280/L), was found to inhibit the biomass, average growth rate and yield to the freshwater green alga, *Pseudokirchneriella subcapitata*, on an acute basis. The RQs for freshwater algae resulting from acute exposure to bicyclopyrone or its formulated product, A16003E, however, did not exceed the LOC at the screening level.

Exposure of bicyclopyrone and a bicyclopyrone formulated product, A15749AD containing 150 g a.i./L, resulted in reduced yield and reduced growth rates in the freshwater vascular plant, duckweed, *Lemna gibba*. Exposure of the bicyclopyrone transformation products, CSAA589691 and CSCC163768, assuming 100% transformation from bicyclopyrone, did not result in any adverse effects to duckweed. The RQs for freshwater vascular plant resulting from acute exposure to bicyclopyrone, its formulated product, A15749AD, and the transformation products (assuming 100% transformation from bicyclopyrone), CSAA589691 and CSCC163768, did not exceed the LOC at the screening level.

Marine/estuarine species: Acute exposure to bicyclopyrone affected the survival of saltwater mysids (*Americamysis bahia* formerly *Mysidopsis bahia*) but did not affect the survival of sheepshead minnow (*Cyprinodon variegatus*). Bicyclopyrone was, however, acutely toxic to the aquatic nonvascular marine diatom (reduced growth rate and yield), *Skeletonema costatum*, and the Eastern oyster (reduced shell growth), *Crassostrea virginica*. The acute RQs for all marine/estuarine species tested, however, did not exceed the LOC at the screening level.

As there were no chronic effects to aquatic fish or invertebrates and the RQs for aquatic organisms other than aquatic plants were less than 0.1, the likelihood that the chronic endpoint for aquatic invertebrates that would exceed the LOC is low. No additional chronic studies of aquatic organisms will be required at this time.

4.2.3 Incident Reports or Special Use Pattern

No incident reports were available. This is a new active ingredient and incident reports are not expected.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Acceptable Efficacy Claims for SYNA16003 Herbicide

Efficacy data were submitted from a total of 15 replicated field trials conducted from 2010 to 2011 at several locations throughout Ontario. Three rates of bicyclopyrone were assessed to determine herbicidal activity. The herbicide treatments were applied using small plot application equipment.

The efficacy of SYNA16003 Herbicide was visually assessed as percent weed control and compared to an untreated weedy check. Observations were made up to two times throughout the growing season (early- and mid-season). The data support the weed control claims summarized in Table 5.1.1.1 when SYNA16003 Herbicide is applied as a pre-emergent or post emergent treatment in corn.

Table 5.1.1.1 Weed Control Claims for SYNA16003 Herbicide

Herbicide Rate	Weeds Controlled or Suppressed	
	Grassy Weeds	**Broadleaf Weeds**
37.5 g a.i./ha	Early-season suppression of proso millet.	Short-season residual control of velvetleaf and eastern black nightshade. Triazine-resistant and Group 2 Resistant weed biotypes will also be controlled.
50 g a.i./ha	Early-season suppression of proso millet.	Short-season residual control of above noted broadleaf weeds plus common ragweed, redroot pigweed and lamb's-quarters. Triazine-resistant and Group 2 Resistant weed biotypes will also be controlled.

5.1.2 Acceptable Efficacy Claims for Acuron Herbicide

A scientific rationale was submitted in support of Acuron Herbicide. The rationale supports the weed control claims summarized in Table 5.1.2.1 when Acuron Herbicide is applied as a pre-emergent or post emergent treatment in corn.

Table 5.1.2.1 Weed Control Claims for Acuron Herbicide

Herbicide Rate	Weeds Controlled or Suppressed	
	Grassy Weeds	**Broadleaf Weeds**
2025 g a.i./ha	Season-long control of barnyard grass, crabgrass (smooth and hairy), fall panicum, foxtail (green, yellow and giant) and witchgrass. Early-season suppression of proso millet.	Season-long control of nightshade (American, eastern black), common ragweed, lady's-thumb, lamb's-quarters, redroot pigweed, velvetleaf, wild buckwheat and wild mustard. Triazine-resistant and Group 2 Resistant weed biotypes will also be controlled.

5.1.3 Herbicide Tank Mix Combinations

5.1.3.1 SYNA16003 Herbicide

Data from a total of 15 replicated field trials conducted from 2010 to 2011 at several locations throughout Ontario were submitted in support of the proposed tank mixes.

The efficacy of SYNA16003 Herbicide plus various tank mix partners was visually assessed as percent weed control and compared to an untreated weedy check. Observations were made up to three times throughout the growing season. The data support the tank mixture of SYNA16003 Herbicide with Primextra II Magnum Herbicide (pre- and post-emergent), Lumax EZ Herbicide (pre- and post-emergent), glyphosate (post-emergent) or glyphosate + Primextra II Magnum Herbicide (post-emergent) in corn for the control of a broader weed spectrum, the control of emerged weeds and/or season-long weed control.

5.1.3.2 Acuron Herbicide

No tank-mix partners were proposed for inclusion on the Acuron Herbicide label.

5.2 Non-Safety Adverse Effects

5.2.1 SYNA16003 Herbicide

Data from five dedicated weed-free crop tolerance trials along with crop tolerance data from 15 efficacy trials conducted from 2010 to 2012 at multiple locations throughout Ontario were submitted in support of the host crop tolerance claims. All dedicated crop tolerance trials included treatments of SYNA16003 Herbicide applied at twice the maximum proposed rate.

Crop injury (%) was visually assessed up to four times during the growing season, and crop yield was reported in one of the dedicated tolerance trials and eight of the efficacy trials.

Crop injury to field corn was acceptable at the maximum application rate of 50 g a.i./ha. While trial data were not provided to support SYNA16003 Herbicide application to seed or sweet corn, application to these other corn types can be supported based on published literature (research findings) for cultivar sensitivity to various Group 27 Herbicides, in addition to the registered use pattern for other Group 27 Herbicides on seed and sweet corn. Furthermore, the possibility for injury to seed and sweet corn will be further mitigated through the inclusion of a precautionary label statement.

5.2.2 Acuron Herbicide

Data from five dedicated weed-free crop tolerance trials conducted in 2012 at multiple locations throughout Ontario were submitted in support of the host crop tolerance claims. All dedicated crop tolerance trials included treatments of Acuron Herbicide applied at twice the maximum proposed rate.

Crop injury (%) was visually assessed up to four times during the growing season, and crop yield was reported in one of the dedicated tolerance trials.

Crop injury to field corn was acceptable at the maximum application rate of 2025 g a.i./ha. Furthermore, tank mix data for SYNA16003 Herbicide + Primextra II Magnum Herbicide + Callisto Herbicide (which has comparable application rates for all four active ingredients to that of Acuron Herbicide) demonstrated acceptable field corn tolerance. While trial data were not provided to support Acuron Herbicide application to seed or sweet corn, application to these other corn types can be supported based on published research findings for cultivar sensitivity to various Group 27 Herbicides, in addition to the registered use pattern for other Group 27 Herbicides on seed and sweet corn. Moreover, the possibility for injury to seed and sweet corn will be further mitigated through the inclusion of a precautionary label statement.

5.2.3 Impact on Succeeding Crops

Rotational crop tolerance data were submitted from 21 trials that were initiated between 4 and 13 months following an application of bicyclopyrone. The number of trials wherein tolerance was evaluated varied by rotational crop. Some trials included multiple varieties/hybrids of one crop. Trials were conducted at various locations throughout Ontario.

5.2.3.1 Acceptable Claims for Rotational Crops for Bicyclopyrone

All available information support a plant back tolerance claim for the following crops planted in the same season (as a salvage crop in the event of crop failure) after an application of bicyclopyrone: field corn, seed corn and sweet corn.

The crop injury and yield data support a rotational crop tolerance claim for the following crop planted in the same season (four months) after an application of bicyclopyrone: winter wheat.

The crop injury and yield data support a rotational crop tolerance claim for the following crops planted in the year following an application of bicyclopyrone: field corn (10 months), seed corn (10 months), sweet corn (10 months), spring wheat (10 months), spring barley (10 months) and soybeans (non-sand based soils; 11 months).

5.3 Consideration of Benefits

5.3.1 Social and Economic Impact

Bicyclopyrone applied prior to weed emergence will provide short season residual control of common lamb's-quarters, redroot pigweed, common ragweed, velvetleaf and Eastern black nightshade, including triazine and Group 2 tolerant biotypes of these weeds, through the critical crop establishment phase of corn (field, seed and sweet) development. Bicyclopyrone will also provide early season suppression of proso millet through the crop establishment phase. This will be unique for corn producers as there are currently no registered herbicides with labelled soil activity on proso millet.

5.3.2 Survey of Alternatives (as of January 2014)

The mode of action of bicyclopyrone is classified as a WSSA Group 27 / HRAC Group F2 inhibitor of HPPD. There are presently five HPPD-inhibiting active ingredients registered in Canada that are found in a total of 20 end-use products (some having additional Herbicide Group active ingredients). Thirteen of the 20 HPPD-inhibitor end-use products are registered for use in corn (field, seed and/or sweet) grown in Eastern Canada.

A number of active ingredients from other Herbicide Groups are registered for pre- and/or post-emergence use in corn grown in Eastern Canada. These active ingredients include compounds that either have contact activity or residual soil activity. Examples of registered active ingredients that provide residual control of broadleaf weeds (like bicyclopyrone) in corn grown in Eastern Canada can be viewed in Table 5.3.2.1.

Table 5.3.2.1 Examples of Herbicides Registered for Use in Corn Grown in Eastern Canada That Have Residual Broadleaf Weed Activity (Note: this is not a comprehensive list).

Herbicide Group	Active Ingredient	Example Product Name	Reg. No.
2	Imazethapyr[1]	Pursuit Herbicide	21537
	Flumetsulam	Broadstrike RC Herbicide	27004
3	Pendimethalin	Prowl 400 EC Herbicide	23439
4	Dicamba	Banvel II Herbicide	23957
4 + 19	Dicamba + diflufenzopyr	Distinct Herbicide	25811
5	Atrazine	Aatrex Liquid 480 Herbicide	18450
	Simazine	Princep Nine-T Herbicide	16370
	Metribuzin	Sencor Solupak	20968
7	Linuron	Lorox L Herbicide	16279
15	Dimethenamid-p	Frontier Max Herbicide	29194
	Flufenacet	Flufenacet 60% Water-Dispersible Granular Herbicide	28293
	Pyroxasulfone	Pyroxasulfone 85 WG Herbicide	30572
	S-metolachlor	Dual II Magnum Herbicide	25729
27	Isoxaflutole	Converge Flexx Herbicide	29071
	Mesotrione	Callisto 480SC Herbicide	27833

[1] Can be applied only to imazethapyr tolerant corn varieties.

Proso millet (the only grass with labelled activity for bicyclopyrone applied alone), is a problematic grassy weed that can be difficult to control with chemical means. At present, there are no active ingredients registered for use in corn that are labelled for residual control of proso millet (in other words, applied to the soil prior to emergence). Options are available for corn growers to control proso millet once it has emerged, many of which require the use of transgenic corn varieties (for example, glyphosate tolerant varieties, glufosinate ammonium tolerant varieties and 2,4-D + glyphosate tolerant varieties). The only products with labelled post-emergence activity against proso millet in corn that do not require the use of transgenic corn varieties include the following Group 2 Herbicides: Ultim 37.4 DF Herbicide (Reg. No. 24682), Ultim 75 DF Herbicide (Reg. No.24736), Tribute Solo 32 DF Herbicide (Reg. No. 27422), Option 2.25 OD Liquid Herbicide (Reg. No. 27424) and Option 35 DF Herbicide (Reg. No. 27425). Accordingly, bicyclopyrone should provide an important alternative to corn growers in

Eastern Canada that have proso millet and want a product that has pre-emergence activity against this troublesome weed.

5.3.3 Compatibility with Current Management Practices Including Integrated Pest Management

The use pattern for SYNA16003 Herbicide is such that multiple weed-control options are available for corn growers, including:

- a two-pass weed control system (residual soil application followed by a planned post-emergent application);
- a one-pass post-emergent system, which would combine the residual capabilities of bicyclopyrone with the burndown ability of a glyphosate tank-mix partner; and
- a one-pass pre-emergent or post-emergent system with Primextra II Magnum Herbicide or Lumax EZ Herbicide.

As a co-formulated product (Acuron Herbicide), season-long control of a number of broadleaf and grassy weeds will be obtained.

The use pattern for both bicyclopyrone products highlights an array of control options available to corn growers, which in turn demonstrates the compatibility of bicyclopyrone with integrated weed management practices.

5.3.4 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Repeated use of herbicides having the same mode of action in a weed control program increases the probability of selecting naturally resistant biotypes. Therefore, SYNA16003 Herbicide and Acuron Herbicide should be used in rotation with herbicides having different modes of action.

5.3.4.1 SYNA16003 Herbicide

Due to the proposed use pattern for SYNA16003 Herbicide, excessive selection pressures for the development of Group 27 Herbicide resistant weeds would not be anticipated. Furthermore, SYNA16003 Herbicide might be a valuable tool for the control of weed biotypes resistant to other herbicide groups (for example, ALS-inhibitors, photosystem II inhibitors and/or EPSPS-inhibitors) that are known to exist in Eastern Canada. Herbicide-resistant populations from 15 weed species have been discovered and are variously resistant to Group 2, 4, 5, 7, 9, and 22. When applied at the labelled use-rates, SYNA16003 Herbicide is expected to control or suppress biotypes of labelled weeds that are resistant to other groups of chemistries. Consequently, bicyclopyrone has the potential to delay the onset of herbicide resistance and to manage certain forms of resistance once present.

The SYNA16003 Herbicide label includes the resistance management statements, as per Regulatory Directive DIR99-06, *Voluntary Pesticide Resistance-Management Labelling Based on Target Site/Mode of Action*.

5.3.4.2 Acuron Herbicide

Although resistant biotypes to Group 5 Herbicides have been documented in a number of weed species found in eastern Canada, there have been no documented cases of resistance to Group 27 or Group 15 Herbicides in Canada. Furthermore, there have been only two weed species worldwide with biotypes documented to have resistance to Group 27 herbicides, and four weed species worldwide with biotypes documented to have resistance to Group 15 Herbicides (including blackgrass [*Alopecurus myosuroides*; Germany], barnyardgrass [*Echinochloa crus-galli*; China, Thailand and Philippines], Italian ryegrass [*Lolium multiflorum*; USA] and rigid ryegrass [*L. rigidum*; Australia]). Given that Acuron Herbicide contains Group 27, Group 15 and Group 5 Herbicide active ingredients, excessive selection pressures for the development of herbicide resistance to any one of these active ingredients would not be anticipated. Moreover, existing herbicide resistant weed biotypes (for example, to Group 5 Herbicides) will be controlled with Acuron Herbicide, provided bicyclopyrone, mesotrione and/or s-metolachor have activity against that particular weed species.

The Acuron Herbicide label includes the resistance management statements, as per Regulatory Directive DIR99-06, *Voluntary Pesticide Resistance-Management Labelling Based on Target Site/Mode of Action*.

5.4 Supported Uses

Refer to Table 14.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances: those that meet all four criteria outlined in the policy, in other words, persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*.

During the review process, bicyclopyrone was assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Bicyclopyrone does not meet all Track 1 criteria, and is not considered a Track 1 substance. See Table below for comparison with Track 1 criteria.
- Bicyclopyrone does not form any transformation products that meet all Track 1 criteria.

Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[6]. The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[8]; and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

Technical grade bicyclopyrone does not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

The end-use products, SYNA16003 and Acuron Herbicide do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02[9].

---

[5] DIR99-03, The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy

[6] *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

[7] NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

[8] DIR2006-02, PMRA Formulants Policy.

[9] DIR2006-02, PMRA Formulants Policy.

Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria			
TSMP Track 1 Criteria	**TSMP Track 1 Criterion only alue**		**Active Ingredient Endpoints**
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]:	Soil	Half-life $\geq$ 182 days	Half-life = 335 days
	Water	Half-life $\geq$ 182 days	Half-life = 681 days
	Sediment	Half-life $\geq$ 365 days	Half-life: stable
	Air	Half-life $\geq$ 2 days or evidence of Long range transport	2 hours
Bioaccumulation[4]	Log $K_{OW} \geq 5$		-1.2 (at pH 7), unlikely to bioaccumulate
	BCF $\geq$ 5000		Not available
	BAF $\geq$ 5000		Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.

[1] All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (in other words, all other TSMP criteria are met).

[2] The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

[4] Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{OW}).

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for bicyclopyrone is adequate to define the majority of toxic effects that may result from exposure. In short-term and chronic studies on laboratory animals, the primary targets were the liver, kidney, eyes and body weight. There was evidence of carcinogenicity in rats and mice after longer-term dosing. A threshold approach was considered appropriate for assessing the cancer risk in humans. There was no evidence of increased susceptibility of the young in the reproduction toxicity study, however, fetal sensitivity was noted in developmental toxicity studies in rats and rabbits, with the rabbits having malformations at a dose that was not maternally toxic. Bicyclopyrone was not considered to be neurotoxic or to have immunotoxic potential. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

The nature of the residues in plants and animals is adequately understood. The residue definition for enforcement is bicyclopyrone and its structurally related metabolites determined as the common moieties SYN503780 and CSCD686480 (expressed as bicyclopyrone equivalents) in plant products and in animal matrices. The proposed uses of bicyclopyrone on field, sweet, popcorn, seed corn and imported sugarcane do not constitute a risk of concern for chronic or acute dietary exposure (food only, and food+water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend MRLs. The PMRA recommends that the following MRLs be specified for residues of bicyclopyrone.

Commodity	Recommended MRL (ppm)
Sweet corn K+CWHR	0.03
Field corn grain, popcorn grain, sugarcane cane	0.02
Meat byproducts of cattle, goats, horses and sheep	1.5
Meat byproducts of hogs	0.20
Meat and fat of cattle, goats, horses, hogs, sheep and poultry; meat byproducts of poultry	0.02
Milk and eggs	0.02

Mixers, loaders, and applicators handling SYNA16003 Herbicide and Acuron Herbicide, and workers re-entering treated corn fields, are not expected to be exposed to levels of bicyclopyrone that will result in a human health concern, when SYNA16003 Herbicide and Acuron Herbicide are used according to label directions and precautions that include wearing the appropriate personal protective equipment.

7.2 Environmental Risk

Bicyclopyrone is moderately persistent in the terrestrial environment. Bicyclopyrone is very highly mobile in soil and may move to groundwater via leaching, and may also move to surface water via spray drift and runoff of dissolved or sorbed residues. In aquatic systems, bicyclopyrone is expected to be moderately persistent. Due to bicyclopyrone's persistence in sediments, annual application is expected to lead to continued accumulation in adjacent aquatic sediments through both spray drift and runoff inputs.

Bicyclopyrone is not expected to bioconcentrate or bioaccumulate in aquatic organisms. Bicyclopyrone does not pose a risk to non-target aquatic organisms, but may post a hazard to non-target aquatic vascular plants, and is unlikely to be consumed in sufficient quantities from feed items to cause adverse effects to wild birds and small wild mammals. The use of bicyclopyrone may pose a risk to terrestrial vascular plants and a hazard to aquatic organisms. Label statements are required on bicyclopyrone end-use products to inform uses of this potential risk/hazard.

7.3 Value

The weight of evidence provided through trial data, rationales and published literature support the proposed uses from a value standpoint. The registration of bicyclopyrone will afford considerable flexibility for the control/suppression of broadleaf and grassy weeds in corn (field, seed and sweet), including the difficult-to-control grassy weed proso millet.

8.0 Proposed Regulatory Decision

Health Canada's Pest Management Regulatory Agency, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Bicyclopyrone Technical, the manufacturing products Bicyclopyrone Wet Paste I and Bicyclopyrone Wet Paste II and the end-use product SYNA16003 Herbicide, containing the technical grade active ingredient bicyclopyrone, to control specific weeds in field, sweet and seed corn. Also proposed for full registration is Acuron Herbicide, containing the active ingredients bicyclopyrone, atrazine, s-metolachlor and mesotrion, to control specific weeds in field, sweet and seed corn.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

µg	micrograms
^{14}C	radiolabelled carbon atom
abs	absolute
AD	administered dose
ADI	acceptable daily intake
a.e.	acid equivalent
a.i.	active ingredient
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
ATPD	Area-treated-per-day
AUC	area under the curve
BBCH	Biologishe Bundesanstalt, Bundessortenamt and Chemical industry
bw	body weight
bwg	bodyweight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
cm	centimetres
DF	dry flowable
DFR	dislodgeable foliar residue
DNA	deoxyribonucleic acid
EC	emulsifiable concentrate
F1	first generation
F2	second generation
fc	food consumption
fe	food efficiency
g	gram
GIT	gastrointestinal tract
ha	hectare(s)
HAFT	highest average field trial
HDPE	High Density Polyethylene
HPLC	high performance liquid chromatography
HPPD	4-hydroxy-phenylpyruvate dioxygenase
hr	hour(s)
HR	hazardous rate
HRAC	Herbicide Resistance Action Committee
ILV	independent laboratory validation
kg	kilogram
K_{ow}	*n*–octanol-water partition coefficient
L	litre
LAFT	lowest average field trial
LC_{50}	lethal concentration 50%
LD	lactation day
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOQ	limit of quantitation

LSC	liquid scintillation counting
MAS	maximum average score
mg	milligram
MIS	maximum irritation score
mL	millilitre
M/L/A	mixer/loader/applicator
MOE	margin of exposure
mol	mole
MRL	maximum residue limit
MS	mass spectrometry
MTD	maximum tolerated dose
NAFTA	North American Free Trade Agreement
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NZW	New Zealand white
P	parental generation
Pa	Pascals
PBI	plantback interval
PET	Polyethylene terephthalate
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
PMRA	Pest Management Regulatory Agency
ppm	parts per million
RBC	red blood cells
RAC	raw agricultural commodity
SC	soluble concentrate
SI	stimulation index
SU	suspension
$t_{1/2}$	half-life
T3	tri-iodothyronine
T4	thyroxine
TAT	tyrosine aminotranferase
TC	transfer coefficient
TLC	thin layer chromatography
TRR	total radioactive residue
UAN	urea ammonium nitrate
US	United States
v/v	volume per volume dilution
WSSA	Weed Science Society of America
wt	weight

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
Plant matrices: Enforcement/Data Gathering Common Moieties Method					
Field corn (forage, ears, grain, stover), wheat (forage, hay, straw, grain), radish (root, top), spinach leaves	GRM030.05A (Original) GRM030.05B (Revised) (Corn Crop field trial, Australian sugarcane crop field trial, Corn processing, field accumulation studies)	The common moieties SYN503780 and CSCD686480	Enforcement/Data gathering: HPLC-MS/MS	GRM030.05A: 0.01 for each of the common moieties expressed as bicyclopyrone equivalents or CSAA915194 equivalents GRM030.05B: 0.01 for each of the common moieties expressed as bicyclopyrone equivalents	PMRA # 2231554, 2231558, 2231567
Extraction solvents:		Acetonitrile/water (80:20 v/v), 30% hydrogen peroxide, 0.05 M sodium hydroxide, and 0.1M hydrochloric acid (pH <5)			
ILV		Matrices: Field corn (grain, forage, stover), and soybean seed			
Radiovalidation		Matrices: Field corn (forage, immature corn grain)			
Plant Matrices: Enforcement/Data Gathering Analyte-Specific Method					

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
Field Corn Grain, Field Corn Mature (dry) Whole Plant, Field Corn Immature (green) Whole Plant, Tomato Fruit, Orange Fruit, Sunflower Seed	GRM030.03A (Storage stability studies for RAC and processed plant commodities)	Analyte-specific: Bicyclopyrone and SYN503780	Data gathering: HPLC-MS/MS	0.01 per analyte	2231553, 2231557, 2231567
Extraction solvents:		Acetonitrile/water (80:20 v/v)			
ILV		Matrices: Field Corn (forage, grain, stover), Soybean Seed			
Radiovalidation		Matrices: Field Corn Forage, Immature Field Corn Grain (Kernel)			
Plant Matrices: Data Gathering Methods for Sugarcane Processing Study					
Cassava Sugarcane Dry Corn Green Corn Green Corn Plant	POPIT MET.116.Rev02 (Brazil processing study)	Analyte-specific: Bicyclopyrone and SYN503780	Data gathering: HPLC-MS/MS	0.01 per analyte	2277280
Extraction solvents:		Acetonitrile/water (80:20 v/v), acetonitrile/water (70:30 v/v)			
Cassava Sugarcane Dry Corn Corn Whole Plant Corn	POPIT MET.117.Rev02 (Brazil processing study)	The common moieties SYN503780 and CSCD686480	Common Moiety Data gathering: HPLC-MS/MS	0.01 for each of the common moieties expressed as bicyclopyrone equivalents or CSAA915194 equivalents	2277281

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
Extraction solvents:		Acetonitrile/water (80:20 v/v), hydrogen peroxide (30%) and 0.05M NaOH, acetonitrile/water (70:30 v/v) for corn and acetonitrile/water (50:50 v/v) for other substrates.			
Animal matrices: Enforcement/Data Gathering Common Moieties Method					
Bovine (milk, liver, kidney, muscle, fat), chicken (whole egg, egg yolk)	GRM030.08A (Original) GRM030.08B (Revised) (Storage stability in animal matrices, livestock feeding study)	The common moieties SYN503780 and CSCD686480	Enforcement/Data Gathering: HPLC-MS/MS	GRM030.08A: 0.01 for each of the common moieties expressed as bicyclopyrone equivalents or CSAA915194 equivalents GRM030.08B: 0.01 for each of the common moieties expressed as bicyclopyrone equivalents	2231564, 2231559, 2231568,
Extraction solvents:		Acetonitrile/ultra-pure water (50:50 v/v), 30% hydrogen peroxide, 0.05 M sodium hydroxide, and 0.1M hydrochloric acid			
ILV		Matrices: Bovine Milk, Liver, Muscle, Chicken Eggs			
Radiovalidation		Matrices: Goat Liver and Chicken Egg Yolk			
Soil	GRM030.02A	Bicyclopyrone	HPLC-MS/MS 400 → 324 *m/z*	0.01 mg/kg	2231575 2231579 2231584
		SYN503780	HPLC-MS/MS 278 →202 *m/z*		
	GRM030.04A	Bicyclopyrone	HPLC-MS/MS 398 → 137 *m/z*		2231578 2231583 2231582
		SYN503780	HPLC-MS/MS 278 → 202 *m/z*		
		CSCC163768	HPLC-MS/MS 234→ 146 *m/z*		
		CSCD656832	HPLC-MS/MS 206 → 142 *m/z*		

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
		CSCD642512	HPLC-MS/MS 398 → 340 m/z		
		CSAA806573	HPLC-MS/MS 220 → 146 m/z		
Water	GRM030.01A	bicyclopyrone	HPLC-MS/MS 400 → 324 m/z	0.01 µg/L	2231585 2231587 2231591
		SYN503780	HPLC-MS/MS 278 →202 m/z		
	GRM030.06A	bicyclopyrone	HPLC-MS/MS 400 → 228 m/z		2231590 2231588
		SYN503780	HPLC-MS/MS 278 → 202 m/z		
		CSCC163768	HPLC-MS/MS 234→ 146 m/z		
		CSCD656832	HPLC-MS/MS 206 → 142 m/z		
		CSCD642512	HPLC-MS/MS 398 → 340 m/z		
		CSAA806573	HPLC-MS/MS 220 → 175 m/z		
Air	GRM030.07A	bicyclopyrone	HPLC-MS/MS 400 → 324 m/z	0.015 µg/m^3	2231594 2231572

Table 2 Toxicity Profile of End-Use Products Containing Bicyclopyrone
(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons.)

Study Type/Animal/PMRA #	Study Results
End-Use Product – SYNA16003	
Acute Oral Toxicity – Up and Down Procedure Wistar rat PMRA 2234547	LD_{50} ♀ > 5000 mg/kg bw **Low acute toxicity**
Acute Dermal Toxicity Wistar rat PMRA 2234549	LD_{50} > 5000 mg/kg bw **Low acute toxicity**
Acute Inhalation Toxicity Wistar rat PMRA 2234550	LC_{50} > 5.08 mg/L **Low acute toxicity**
Eye Irritation Study NZW rabbit PMRA 2234554	$MIS_{(1\ hr)} = 8.67$ $MAS_{(24\text{-}72\ hr)} = 2.44$ **Minimally irritating**
Dermal Irritation Study NZW rabbit PMRA 2234552	$MAS_{(24\text{-}72\ hr)} = 0$ **Non-irritating**
Dermal Sensitization Study – Buehler Method Dunkin Hartley guinea pig PMRA 2234556	**Potential Sensitizer**
End-Use Product – Acuron Herbicide	
Acute Oral Toxicity – Up and Down Procedure Sprague-Dawley rat PMRA 2233218	LD_{50} ♀ = 1750 mg/kg bw **Slight acute toxicity**

Study Type/Animal/PMRA #	Study Results
Acute Dermal Toxicity Sprague-Dawley rat PMRA 2233220	$LD_{50} > 5000$ mg/kg bw **Low acute toxicity**
Acute Inhalation Toxicity Sprague-Dawley rat PMRA 2233222	$LC_{50} > 2.59$ mg/L **Low acute toxicity**
Eye Irritation Study NZW rabbit PMRA 2233226	$MIS_{(1\ hr)} = 16.67$ $MAS_{(24\text{-}72\ hr)} = 11.11$ **Minimally irritating**
Dermal Irritation Study NZW rabbit PMRA 2233224	$MAS_{(24\text{-}72\ hr)} = 3.6$ **Moderately irritating**
Dermal Sensitization Study – Local Lymph Node Assay CBA/J mouse PMRA 2233228	**Potential Sensitizer**

Table 3 Toxicity Profile of Technical Bicyclopyrone
(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted.)

Study Type/Animal/PMRA #	Study Results
Toxicokinetics	Pyridinyl-3-^{14}C bicyclopyrone was the label used for the studies. For the single dose studies 2 or 200 mg/kg bw were used and for the repeat oral dosing, 2 mg/kg bw/day was used. In plasma and blood, T_{max} occurred within 3 hours in all dose groups, indicating rapid absorption. Elimination was found to be bi-phasic. The ά half-life in plasma was 2.4-3.2 hrs in the low and high-dose groups. The β half-life was estimated at 12.5 and 68.6 hrs in males and females, respectively. Plasma AUC analysis suggests 97% and 85% bioavailability for males and females, respectively. AUC values were roughly proportional to dose.

Study Type/Animal/PMRA #	Study Results
	Concentration of radioactivity in blood was similar to plasma suggesting no preferential uptake into red blood cells (RBCs). The highest concentrations for low dose administration were seen in the liver, the gastrointestinal tract (GIT) and kidney. At the high-dose radioactive concentrations were highest in GIT, plasma, blood and liver. The results in males and females were comparable. In the repeat dose groups, the total recovery was >95% AD. The excretion profile was similar between the single and repeat dose studies. Most of the dose was excreted within the first 24 hours (>80% AD). Excretion was similar in males and females, though fecal elimination was higher in males (27% vs. 5%). Urine excretion was 64% and 85% in males and females, respectively. A bile study showed 16% and 2% elimination of AD for males and females, respectively. There were no radioactive residues in expired air. The highest levels of radioactivity were found in the liver (4% and 3% of the AD in males and females, respectively) and kidney (0.3% and 0.4% of the AD). Bicyclopyrone was not extensively metabolized, unchanged parent was the principal radiolabelled component in all dose groups in urine. The majority of the metabolites were created via hydroxylation and O-demethylation reactions. Minor metabolites involved glycine conjugation and cleavage between the pyridinyl and bicyclic rings. The metabolic profile was similar between single dose and multiple low dose. Additionally, the metabolite profile in urine was similar between bile duct cannulated rats and intact rats. Males metabolized a higher proportion of parent compound than females.
Acute Oral Toxicity – Up & Down Procedure Wistar Rat DACO 4.2.1 PMRA 2231610	LD_{50}♀ > 5000 mg/kg bw Low acute toxicity
Acute Dermal Toxicity Wistar Rat DACO 4.2.2 PMRA 2231613	LD_{50} > 5000 mg/kg bw Low acute toxicity

Study Type/Animal/PMRA #	Study Results
Acute Inhalation Toxicity Wistar rat DACO 4.2.3 PMRA 2231617	$LC_{50} > 5.2$ mg/L Low acute toxicity
Primary Eye Irritation NZW rabbit DACO 4.2.4 PMRA 2231627	$MIS_{(1\ hr)} = 5.33/110$ $MAS_{(24\text{-}72\ hr)} = 1.33/110$ Minimally irritating
Primary Dermal Irritation NZW rabbit DACO 4.2.5 PMRA 2231623	$MAS_{(24\text{-}72\ hr)} = 0/8$ Non-irritating
Dermal Sensitization – Local Lymph Node Assay CBA mouse DACO 4.2.6 PMRA 2231630	SI < 3 at all doses Non-sensitizer
14-Day Dietary Toxicity Study Wistar rat PMRA 2231671 Range-finding	Supplemental ≥ 0.5 ppm A clear dose response ↑ bicyclopyrone and tyrosine plasma concentrations.
90-Day Dietary Study CD-1mouse PMRA 2231638	NOAEL = 1127/1343 mg/kg bw (♂/♀) LOAEL not established ≥ 542.6/808.5 mg/kg bw/day (♂/♀) Increased liver weight accompanied by minimal centrilobular hepatocyte hypertrophy (non-adverse)

Study Type/Animal/PMRA #	Study Results
13-Week Dietary Study (2009) Wistar rat PMRA 2231636	NOAEL = 0.72/0.88 mg/kg bw/day (♂/♀) LOAEL = 183/229 mg/kg bw/day (♂/♀) based on ↑ incidence of eye opacity, ↑ocular keratitis; ↓ bw and bwg (♂).
28-Day Capsule Study Beagle dog PMRA 2231632	Range-finding ≥ 10 mg/kg bw/day ↑ urine phenolic acid concentrations and plasma tyrosine 250 mg/kg bw/day Moderate hypoactivity, slightly unsteady gait, increased heart rate, regurgitation, salivation, ↓ bw, fc, moderate retinopathy characterised by fluid effusion in the outer choroid of one eye, swelling and vacuolation of the retinal pigment epithelium, minimal inflammatory cell infiltration at the choroidal/retinal junction and partial retinal detachment and ↓ reduced cortical lymphocytes in the thymus (♂). Group terminated day 7 as MTD exceeded.
13-Week Capsule Study Beagle dog PMRA 2231642	NOAEL = 125 mg/kg bw/day LOAEL not established
52-Week Capsule Study Beagle Dog PMRA 2231646	NOAEL = not established LOAEL = 2.5 mg/kg bw/day based on chromatolysis/swelling of selected neurons in dorsal root ganglia and ↑ incidence of degeneration of sciatic nerve fibres.
28-Day Dermal Toxicity Study Wistar rat PMRA 2276026	NOAEL = 50 mg/kg bw/day (♂/♀) LOAEL = 250 mg/kg bw/day (♂/♀) based on corneal degeneration; ↑ absolute liver and kidney weight (♂).
80-Week Dietary Toxicity Study CD-1 mouse PMRA 2231668	NOAEL = 233/242 mg/kg bw/day (♂/♀) LOAEL = 940/1027 mg/kg bw/day (♂/♀) based on ↓ bw, bwg, fe; ↑ incidence of bronchio-alveolar carcinoma and bronchio alveolar adenoma (♂).

Study Type/Animal/PMRA #	Study Results
104-Week Dietary Toxicity Study Han Wistar rat PMRA 2231665	NOAEL = not determined/0.28 mg/kg bw/day (♂/♀) LOAEL (♂) = 0.28 mg/kg bw/day based on ↑ incidence thyroid follicular hypertrophy and chronic progressive nephropathy in the kidney LOAEL (♀) = 35 mg/kg bw/day based on ↑ incidence of opaque eyes (98-100%), corneal damage, eye keratitis and incidence of regenerative corneal hyperplasia and ↓ abs. brain wt.
Multigenerational Dietary Reproductive Toxicity Study Wistar rat PMRA 2231681 Range-finding	Range-finding study Parental Toxicity ≥ 25 ppm vascular corneal opacity ≥ 500 ppm *non adverse:*↑ liver wt, ↑ kidney wt ≥ 2500 ppm ↓bwg (♀); 5000 ppm ↓ bwg (♂); ↓ bw (♀) Reproductive toxicity: ≥ 2500 ppm ↓ litter size, ↓ uterine implantation scars Offspring toxicity: ≥ 500 ppm ↓ bw, ↓ bwg, corneal opacity (F1)
Multigenerational Dietary Reproductive Toxicity Study Wistar rat PMRA 2231684	Parental Toxicity: NOAEL = not established LOAEL = 1.9/2.5 mg/kg bw/day (♂/♀) based on vascular keratitis, corneal opacity and roughness (P♂, F1) and kidney pelvic dilation (P, F1). Reproductive toxicity: NOAEL = 38.4/49.5 mg/kg bw/day (♂/♀) LOAEL = 377/501 mg/kg bw/day (♂/♀) based on ↓ precoital interval (P)(♀); ↓ sperm velocities (actual path, straight line)and ↑ incidence of abnormal sperm (♂). Offspring toxicity: NOAEL = 1.9/2.5 mg/kg bw/day (♂/♀)

Study Type/Animal/PMRA #	Study Results
	LOAEL = 38.4/49.5 mg/kg bw/day (♂/♀) based on ↓bw (F2), ↓bwg (F1, F2), corneal opacity and roughness (F1, F2) and vascular keratitis (F1, F2).
Developmental Gavage Toxicity Study Wistar rat PMRA 2231686	Range-finding Maternal toxicity ≥ 100 mg/kg bw/day: ↓ bwg (transient) ≥ 500 mg/kg bw/day: ↓ fc (Days 5-8, 8-11, 11-14, and 14-17; *non-adverse*) Developmental toxicity ≥ 100 mg/kg bw/day: ↑ Non-ossified cervical vertebra, ↑ full or rudimentary supernumerary ribs, ↑ long costal cartilage ≥ 500 mg/kg bw/day: ↓ fetal bw (6-10 %), ↑ pelvic girdle displaced, ↑ costal cartilage asymmetrically aligned at the sternum 1000 mg/kg bw/day: ↑ Supernumerary costal cartilage
Developmental Gavage Toxicity Study Wistar rat PMRA 2231688	Maternal toxicity NOAEL = 1000 mg/kg bw/day LOAEL not established Developmental toxicity NOAEL = not established LOAEL = 100 mg/kg bw/day based on ↑ incidence of malpositioned pelvic girdle (caudal) (variation), full or rudimentary supernumerary ribs, long costal cartilage and non-ossified cervical vertebra. Evidence of sensitivity of the young
Developmental Gavage Toxicity Study NZW rabbit PMRA 2231691	Range-finding Maternal toxicity: 500 mg/kg bw/day: One death day 8, one sacrificed moribund day 8, ↓ bw and bwg and clinical signs (pinched in sides, reluctance to move, irregular breathing and subdued behavior). Group terminated day GD8. 100 & 200 mg/kg bw/day No treatment related findings. Developmental toxicity:

Study Type/Animal/PMRA #	Study Results
	200 mg/kg bw/day ↑ incidence of skeletal variations (lengthened costal cartilage on rib 10, rib 13 (extra rib of long length attached to vertebral column) and 27 prepelvic vertebrae.
Developmental Gavage Toxicity Study (2012a) NZW rabbit PMRA 2231994	Range-finding Maternal toxicity ≥ 10 mg/kg bw/day ↑ plasma L-tyrosine levels and dose proportional ↑ in plasma levels of bicyclopyrone during gestation with NOA454598 (livestock and plant metabolite) present at approx. 5% of parent. ≥ 250 mg/kg bw/day ↑ mortality, moribundity and abortion, ↓ bw, bwg and fc. Group terminated days 7-8 due to excessive toxicity. Developmental toxicity 50 mg/kg bw/day ↑ incidence of 13th full rib and 27 presacral vertebrae
Developmental Gavage Toxicity Study NZW rabbit PMRA 2231709	Range-finding Maternal Toxicity ≥100 mg/kg bw/day Dose proportional ↑ plasma tyrosine levels and plasma levels of parent bicyclopyrone 200 mg/kg bw/day bw loss days 21-29 Developmental Toxicity ≥ 100 mg/kg bw/day ↑ incidence of 13th full rib and 27 presacral vertebrae ≥150 mg/kg bw/day ↑ incidence of extra site of ossification ventral to cervical centrum no. 2 200 mg/kg bw/day ↓ bw
Developmental Gavage Toxicity Study NZW rabbit	Maternal toxicity: NOAEL = 50 mg/kg bw/day 200 mg/kg bw/day: mortality/moribundity (7 dead/ killed *in extremis*, days 22-28), ↓ fc (days 21-29), ↓ bwg (Days 13-21) , mean bw loss (Days 21-29)

Study Type/Animal/PMRA #	Study Results
PMRA 2231697	Tyrosine concentration in the plasma increased with dosing at 10 mg/kg bw/d, without dose proportionality. Developmental toxicity: NOAEL = not established ≥ 10 mg/kg bw/day: ↑incidence of 13th full rib, ↑ 27 presacral vertebrae Evidence of sensitivity of the young
Developmental Gavage Toxicity Study Himalayan rabbit PMRA 2231700	Range-finding Maternal Toxicity 250 mg/kg bw/day ↑ post-implantation loss Developmental Toxicity ≥50 mg/kg bw/day Interventricular septal defect, ↑ incidence of supernumerary ribs and supernumerary costal cartilage 250 mg/kg bw/day Hydrocephaly (1 fetus), ↑ incidence of cervical vertebra fused to exoccipital, cervical vertebra supernumerary ventral arch, cervical vertebral body/arch misshaped/fused cervicothoracic vertebrae and thoracolumbar vertebrae with additional hemivertebra, and rib and /or costal cartilage absent, interrupted or short, incompletely or non-ossified sternebra 1 and costal cartilage 1 not reaching the sternum.
Developmental Gavage Toxicity Study Himalayan rabbit PMRA 2231704	Maternal Toxicity NOAEL = 50 mg/kg bw/day LOAEL = 250 mg/kg bw/day based on macroscopic findings of the stomach wall (reddening, red stripes or crateriform raised areas) and ↑ incidence of post-implantation loss. Developmental Toxicity: NOAEL not established LOAEL = 10 mg/kg bw/day based on ↑ incidence of interventricular septum variations, unilateral missing kidney and ureters and an abnormal heart perimembraneous region (abnormal surface). - malformation ≥ 50 mg/kg bw/day ↑ incidence of malpositioned pelvic girdle (variation), 27 pre-sacral vertebra, supernumerary ribs, costal cartilage changes) 250 mg/kg bw/day ↑ incidence of cervical vertebral ossification changes, ↓ mean litter weight

Study Type/Animal/PMRA #	Study Results
	Evidence of teratogenicity Evidence of sensitivity of the young
Developmental Gavage Toxicity Study (2012b) Himalayan rabbit PMRA 2231707	Maternal toxicity: NOAEL = 10 mg/kg bw/day LOAEL = 250 mg/kg bw/day based on mMortality (2 dams were sacrificed on day 22), red/dark red foci in stomach of the 2 sacrificed dams, ↓ bwg and ↑ post-implantation loss. Developmental toxicity: NOAEL = 1 mg/kg bw/day LOAEL = 10 mg/kg bw/day based on ↑ full supernumerary thoracolumbar ribs, slowed costal cartilage development (↑ costal cartilage 1 not reaching sternum right and ↓ costal cartilage 2 not reaching sternum left) 250 mg/kg bw/day: ↓ fetus wt, ↑ fetal incidence of jaw/palate cleft heart abnormalities (aortic arch narrow, aortic arch dilated, pulmonary trunk/ductus arteriosus threadlike or absent with or without heart misshapen, aortic arch and descending aorta right-sided, innominate and subclavian arteries origins transposed, aortic arch right sided, descending right-sided and with supernumerary branch, pulmonary trunk/ductus arteriosus retro-oesophageal, subclavian arteries origins malpositioned, pulmonary trunk/ductus arteriosus narrow, subclavian artery arising from pulmonary trunk), uterine horn absent/threadlike or ovary misshapen, ↑ oesophagus malpositioned, ↑ cervical vertebral irregularities, ↑ rib/costal cartilage abnormalities (fused/interrupted/short), skeletal variations (↑ cervical vertebrae structural variations, ↑ cervical vertebrae ossification irregularities, ↑ caudal displacement of pelvic girdle), ↑ incompletely ossified pubis, ureter and kidney missing. Evidence of sensitivity of the young
Bacterial Reverse Mutation Assay (2007) *S. typhimurium* & *E. coli* PMRA 2231653	Negative
Bacterial Reverse Mutation Assay (2010) *S. typhimurium* & *E. coli* PMRA 2231655	Negative

Study Type/Animal/PMRA #	Study Results
In Vitro Mammalian Cell Assay Mouse lymphoma L5178Y cells PMRA 2231659	Negative
In Vitro Mammalian Clastogenicity Assay Chromosome Aberration PMRA 2231657	Negative
Bone Marrow Micro Nucleus Assay Wistar rat PMRA 2231661	Negative
In vivo Unscheduled DNA Synthesis Assay Wistar rat PMRA 2231663	Negative
Acute Gavage Neurotoxicity Study Crl:CD(SD) rat PMRA 2231718	Range-finding No adverse effects were observed at the highest dose tested.
Acute Gavage Neurotoxicity Study Crl:CD(SD) rat PMRA 2231716	NOAEL = 200/2000 mg/kg bw (♂/♀) LOAEL not established ≥200 mg/kg bw Day 0 only: ↓ motor activity, ↓ mean ambulatory counts No evidence of neurotoxicity

Study Type/Animal/PMRA #	Study Results
28-Day Dietary Neurotoxicity Study Crl:CD(SD) rat PMRA 2231725 Range-finding	Range-finding ≥ 240/259 mg/kg bw/day (♂) ↓ bwg (16%), ↓ fc ((*non-adverse*) 471/505 mg/kg bw/day: ↓ bw (21/23% ; ♂/♀)
90-Day Dietary Neurotoxicity Study Crl:CD(SD) rat PMRA 2231720	NOAEL = not established/415 mg/kg bw/day (♂/♀) LOAEL (♂) = 4 mg/kg bw/day based on unilateral or bilateral keratitis. LOAEL (♀) not established
28-Day Dietary Immunotoxicity Study Crl:CD-1(ICR) mouse PMRA 2231608 Antibody Plaque Forming Cells Assay	NOAEL = 1192 mg/kg bw/day LOAEL not established No evidence of immunotoxic potential.
Effect on Rat Thyroid Peroxidase Activity In Vitro Wistar rat PMRA 2231673	Supplemental Treatment with bicyclopyrone had no significant effect on rat thyroid peroxidase activity at any concentration tested.
28-Day Dietary Thyroid Mode of Action Study Crl:WI(Han) rat PMRA 2231674	Supplemental ≥ 0.5 mg/kg bw/day Dose and time dependent ↑ tyrosine levels and ↓ T_4 levels, fc, ↑ liver weight ≥ 41.5 mg/kg bw/day Dose and/or time dependent ↑hepatic UDGPT activity, ↓ T_3, bw and bwg, ↑ incidence of thyroid follicular cell hypertrophy 400 mg/kg bw/day ↑ incidence of hepatocellular centrilobular hypertrophy

Table 4 Toxicology Endpoints for Use in Health Risk Assessment for Bicyclopyrone

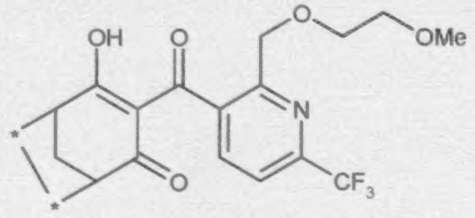
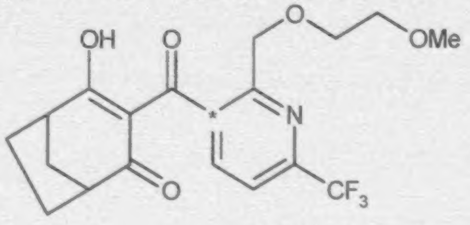
Exposure Scenario	**Study**	**Point of Departure and Endpoint**	**CAF[1] or Target MOE**
Acute dietary general population	Acute neurotoxicity study in rats	NOAEL = 200 mg/kg bw/day Decreased motor activity and mean ambulatory counts (♂)	100
	ARfD = 2.0 mg/kg bw		
Acute dietary females 13-49 years of age	Rabbit Developmental Toxicity Studies	NOAEL (malformations) = 1 mg/kg bw/day Missing kidney and ureter in fetuses	1000
	ARfD = 0.001 mg/kg bw		
Repeated dietary	2 yr rat dietary study	LOAEL = 0.28 mg/kg bw/day Increased severity and incidence of thyroid follicular hypertrophy and chronic progressive nephropathy in the kidney	300
	ADI = 0.001 mg/kg bw/day		
Short term to intermediate dermal[2]	Rabbit Developmental Toxicity Studies	NOAEL (malformations) = 1 mg/kg bw/day Missing kidney and ureter	1000
Short term to intermediate inhalation[3]	Rabbit Developmental Toxicity Studies	NOAEL (malformations) = 1 mg/kg bw/day Missing kidney and ureter	1000
Cancer	Cancer risk (threshold) was addressed through the selected toxicology endpoints.		

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational assessments

[2] Since an oral NOAEL was selected, a dermal absorption factor was used in a route-to-route extrapolation

[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 5 Integrated Food Residue Chemistry Summary

<table>
<tr><th colspan="5">NATURE OF THE RESIDUE IN FIELD CORN</th><th colspan="2">PMRA # 2231735</th></tr>
<tr><td>Radiolabel Positions</td><td colspan="4">[Bicyclooctenone-6,7-14C2]-bicyclopyrone
</td><td colspan="2">[Pyridine-3-14C]-bicyclopyrone
</td></tr>
<tr><td>Test Variety</td><td colspan="6">Zea mays cv Carella 2910</td></tr>
<tr><td>Test Site</td><td colspan="6">Plants grown in outdoor containers</td></tr>
<tr><td>Treatment</td><td colspan="6">Treatment 1: A single pre-emergence spray treatment
Treatment 2: A single pre-emergence spray treatment, followed by a post-emergence (8-9 leaf growth stage) spray treatment</td></tr>
<tr><td>Total Rate</td><td colspan="6">Treatment 1: 200 g a.i./ha
Treatment 2: 1 × 200 g a.i./ha (pre-) and 1 × 200 g a.i./ha (post-); total rate of 400 g a.i./ha</td></tr>
<tr><td>Formulation</td><td colspan="6">250 g/L EC formulation</td></tr>
<tr><td>Preharvest interval</td><td colspan="6">Forage: 55 days (BBCH 75-79 growth stage)
Stover, Cob, Grain: 99 days (BBCH 89 growth stage)</td></tr>
<tr><td colspan="3">Analytical Method Overall Total Radioactive Residues (TRR) Identification & Characterization</td><td colspan="4">Combustion/Liquid Scintillation Counting (LSC)
Thin-Layer Chromatography (TLC); LC-MS/MS</td></tr>
<tr><td colspan="3">Extraction Solvents</td><td colspan="4">Acetonitrile:Water (4:1, v/v); Acetonitrile:Water (3:7, v/v); Acetonitrile</td></tr>
<tr><td colspan="3">Post-Extraction Solids</td><td colspan="4">0.1M HCl at 40°C for 4 hrs; 1M HCl at 40°C for 4 hrs</td></tr>
<tr><td colspan="3">Storage Interval (harvest to analysis) ≤-20°C</td><td colspan="4">Analysis within 5-6 months of sampling. Re-analysis of original fractions after 16 months showed no significant change in profile.</td></tr>
<tr><td rowspan="3">Matrices</td><td rowspan="3">Growth Stage at Harvest</td><td rowspan="3">PHI (days)</td><td colspan="2">[Bicyclooctenone-6,7-14C2]</td><td colspan="2">[Pyridine-3-14C]</td></tr>
<tr><td colspan="2">Overall TRRs (ppm), expressed as parent equivalents</td><td colspan="2">Overall TRRs (ppm), expressed as parent equivalents</td></tr>
<tr><td>Pre-emergent</td><td>Pre-emergent + Post-emergent</td><td>Pre-emergent</td><td>Pre-emergent + Post-emergent</td></tr>
<tr><td>Field Corn Forage (immature stalks + surrounding leaves)</td><td>BBCH 75-79</td><td>55</td><td>0.022</td><td>0.444</td><td>0.083</td><td>0.877</td></tr>
<tr><td>Field Corn Grain</td><td>BBCH 89</td><td>99</td><td>0.003</td><td>0.059</td><td>0.005</td><td>0.028</td></tr>
</table>

Field Corn Stover (mature stalks + surrounding leaves)	BBCH 89	99	0.036	0.465	0.082	0.845
Field Corn Cobs (mature ears minus grain and minus surrounding leaves)	BBCH 89	99	0.002	0.034	0.004	0.019

The overall TRR reported represent direct quantification by LSC. Overall residues of parent equivalents were much higher following combined pre-emergent and post-emergent treatments on field corn than from a single pre-emergent use for both radiolabels. The same major identified/characterized metabolites were found in both application regimes.

Metabolites Identified/Characterized	Major Metabolites (>10% of the TRRs)	
Radiolabel Position	[Bicyclooctenone-6,7-14C2]	[Pyridine-3-14C]

The major and minor metabolites are comprised of hydroxylated metabolites present in both the free and glycoside conjugated forms, including monohydroxylated and dihydrohydroxylated bicyclopyrone isomers. There were also metabolites which retained only the pyridine ring (CSCD686480, CSCD686481, CSAA806573, and CSCD656832) that were detected in forage and/or stover. There was also evidence of a metabolite derived specifically from the bicyclooctenone ring system (CSAA589691) predominantly detected in field corn grain and cob.

Field Corn Grain	CSAA589691	Desmethyl monohydroxy bicyclopyrone isomers, monohydroxy bicyclopyrone isomers
Field Corn Stover	Desmethyl monohydroxy bicyclopyrone isomers, desmethyl dihydroxy bicyclopyrone isomers	Desmethyl monohydroxy bicyclopyrone isomers, desmethyl dihydroxy bicyclopyrone isomers
Field Corn Forage	Desmethyl monohydroxy bicyclopyrone isomers, desmethyl dihydroxy bicyclopyrone isomers	Desmethyl monohydroxy bicyclopyrone isomers, desmethyl dihydroxy bicyclopyrone isomers
Field Corn Cob	CSAA589691	None

NATURE OF THE RESIDUE IN SUGARCANE	PMRA # 2231733
Radiolabel Position	[Bicyclooctenone-6,7-14C2] and [Pyridine-3-14C]
Test Variety	*Saccharum officinarum* cv NC0310
Test Site	Plants initially grown in outdoor containers, then moved to glasshouse to avoid cold temperatures
Treatment	A single foliar application at 7-8 leaf growth stage
Total Rate	314 g a.i./ha [Bicyclooctenone-6,7-14C2] and 304 g a.i./ha [Pyridine-3-14C]
Formulation	250 g/L EC formulation
Preharvest interval	42 days (immature foliage); 301 days (mature foliage and sugarcane cane)
Analytical Method Overall TRR Identification & Characterization	Combustion/LSC TLC; LC-MS/MS

Extraction Solvents	Acetonitrile:Water (4:1, v/v); Acetonitrile:Water (3:7, v/v); Acetonitrile
Post-Extraction Solids	0.1M HCl at 40°C for 2 hrs; 1M HCl at 40°C for 2 hrs
Storage Interval (harvest to analysis) ≤-20°C	Analysis within 1 month of harvest. Re-analysis of original fractions after 14 months showed no significant change in profile.

Matrices	Growth Stage at Harvest	PHI (days)	[Bicyclooctenone-6,7-14C2]	[Pyridine-3-14C]
			Overall TRRs (ppm), expressed as parent equivalents	Overall TRRs (ppm), expressed as parent equivalents
Immature Foliage	BBCH 23-24	42	0.809	1.048
Mature Foliage	BBCH 39	301	0.004	0.003
Mature Sugarcane Cane	BBCH 39	301	0.002	0.004

Mature cane and foliage were not further extracted since residues were less than 0.01 ppm.

Metabolites Identified/Characterized	Major Metabolites (>10% of the TRRs)	
Radiolabel Position	[Bicyclooctenone-6,7-14C2]	[Pyridine-3-14C]

The parent was not detected in the sugarcane foliage samples taken 42 days after treatment. The major and minor metabolites are comprised of hydroxylated metabolites present in both the free and glycoside conjugated forms, including monohydroxylated and dihydrohydroxylated bicyclopyrone isomers. Additional metabolites of the parent were detected that contained only the pyridine ring, which were present as both the free form and the glycoside forms (CSCD686480 and CSCD686481).

Immature Foliage (42 day PHI)	CSCD675162, CSCD677693; CSCD677306 glycoside	CSCD686480 glycoside; CSD677693; CSCD677306 glycoside

NATURE OF THE RESIDUE IN CONFINED ROTATIONAL CROPS	**PMRA # 2231764**

EXPERIMENTAL DESIGN

Crop/crop group/Variety	Rate (g a.i./ha)	PBI* (days)	Growth stage at harvest	Harvested RAC	Harvesting Procedure
Spring Wheat/Small grain/ Tybalt	350	30 (B,P), 120 (B, P), 270 (B,P)	BBCH 22-23	Forage	Samples were collected by hand by cutting the stalks 1cm above the soil surface. Wheat harvested at the hay stage was left to dry in a glasshouse under ambient temperature for 2-3 days. At maturity, the intact ears were separated into chaff using an ear thresher. The forage, hay and straw were chopped into 10 cm long pieces.
			BBCH 43-47	Hay	
			BBCH 89	Straw and grain	
Spinach/Leafy vegetable/ Bella	200	120 (B,P)	BBCH 48-49	Mature Stage	Samples were collected by hand by cutting the stem at the soil

F		180 (B,P)			surface and removing any soil particles with tissue. The leaves were chopped into 6 cm long strips.
	350	120 (P) 180 (B,P)			
Turnips/Root crop/ Tokyo Cross	200	60-root (B,P) 60 - foliage (B,P) 270 – foliage (B,P)	BBCH 48-49	Leaves and roots	Samples were collected by hand by cutting the stem at the shoot/root junction. Fibrous roots were removed from the tubers and discarded, and the tubers were cleaned free of soil. The leaves were chopped into 6 cm long strips and the tubers into 2-3 cm wide pieces.
	350	60-root (B,P) 60- foliage (B,P) 270- foliage (B,P)			

B =[Bicyclooctenone-6,7-14C2]-bicyclopyrone; P = [Pyridine-3-14C]-bicyclopyrone

Storage Interval (harvest to analysis) ≤-10°C	Analysis of spring wheat within 1-4 months of sampling. Re-analysis of original fractions after 16-18 months showed no significant change in profile.

Overall TRR in Rotational Crops.

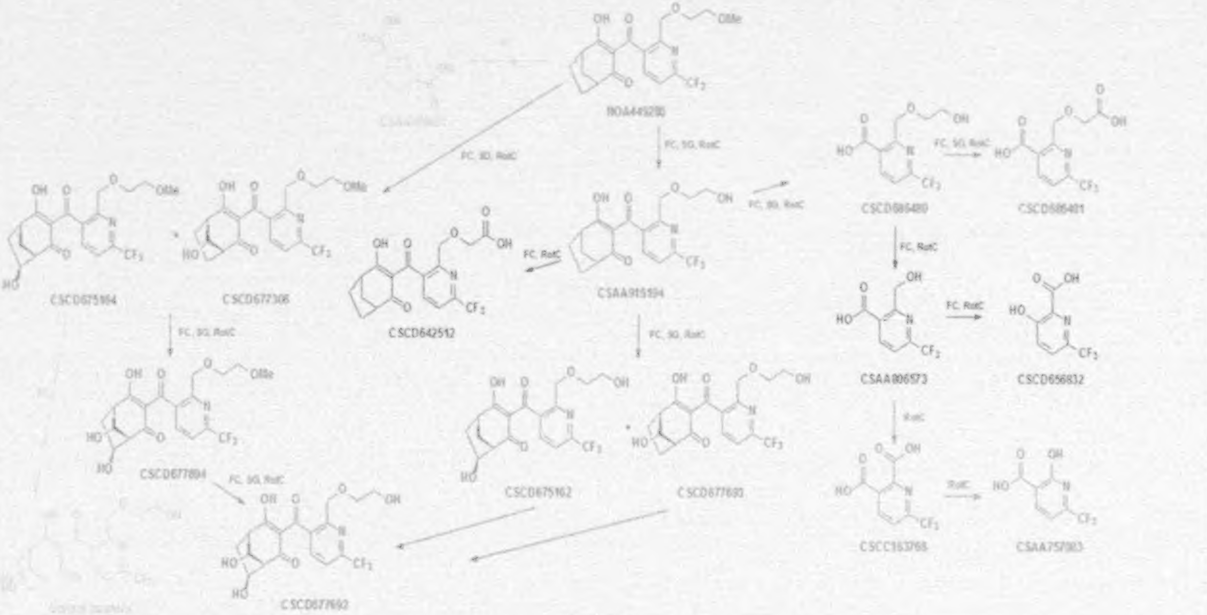
Matrices	Growth Stage at Harvest	PBI (days)	Applic. Rate (g a.i./ha)	[Bicyclooctenone-6,7-14C2]	[Pyridine-3-14C]
				Overall TRRs (ppm), expressed as parent equivalents	
Spring wheat forage	BBCH 22-23	30	350	0.068	0.088
		120	350	0.046	0.074
		270	350	0.010	0.048
Spring wheat hay	BBCH 43-47	30	350	0.348	0.516
		120	350	0.097	0.248
		270	350	0.044	0.160
Spring wheat straw	BBCH 89 (maturity)	30	350	0.445	0.497
		120	350	0.108	0.299
		270	350	0.048	0.183
Spring	BBCH 89	30	350	0.181	0.196

wheat grain	(maturity)	120	350	0.061	0.175
		270	350	0.029	0.061
Turnip foliage	BBCH 48-49 (maturity)	60	200	0.015	0.019
		60	350	0.021	0.016
		270	200	0.006	0.009
		270	350	0.011	0.016
Turnip Root	BBCH 48-49	60	200	0.010	0.009
		60	350	0.012	0.009
Spinach Foliage	BBCH 48-49 (maturity)	120	200	0.008	0.032
		120	350	Not determined	0.016
		180	200	0.008	0.005
		180	350	0.004	0.007
Overall residues less than LOQ (<0.01 ppm) at the various PBI were not further identified and characterized.While samples were taken at PBIs of 30, 120 and 270 days for all crops, samples from PBIs not shown were either not harvested due to phytotoxicity, or were not analysed due to low overall TRR.					

Metabolites Identified/Characterized		Major Metabolites (>10% of the TRRs)	
Matrices	PBI (days)	[Bicyclooctenone-6,7-14C2]	[Pyridine-3-14C]
Selected hydroxylated metabolites were present in both the free and glycoside conjugated forms.			
Wheat forage	30	Desmethyl monohydroxy bicyclopyrone isomers; monohydroxy bicyclopyrone isomers	CSCD686480; desmethyl monohydroxy bicyclopyrone isomers; monohydroxy bicyclopyrone isomers
	120	Desmethyl monohydroxy bicyclopyrone isomers; monohydroxy bicyclopyrone isomers	CSCD656832; desmethyl monohydroxy bicyclopyrone isomers; monohydroxy bicyclopyrone isomers
	270	None	CSCD656832 + conjugate, CSCD686480 glycoside
Wheat hay	30	Desmethyl monohydroxy bicyclopyrone isomers; monohydroxy bicyclopyrone isomers + monohydroxy bicyclopyrone glycoside (isomers)	CSCD686480; Desmethyl monohydroxy bicyclopyrone isomers; monohydroxy bicyclopyrone isomers + monohydroxy bicyclopyrone glycoside (isomers)
	120	Desmethyl monohydroxy bicyclopyrone isomers; monohydroxy bicyclopyrone isomers	CSCD656832 + conjugate; CSCD686480; desmethyl monohydroxy bicyclopyrone isomers; monohydroxy bicyclopyrone isomers
	270	Monohydroxy bicyclopyrone isomers	CSCD656832; CSCD686480
Wheat grain	30	Monohydroxy bicyclopyrone isomers	None

	120	None	None
	270	None	CSCD656832; CSCD686480
Wheat straw	30	CSCD677694; Desmethyl monohydroxy bicyclopyrone isomers; monohydroxy bicyclopyrone isomers + monohydroxy bicyclopyrone glycoside (isomers)	CSCD686480; Desmethyl monohydroxy bicyclopyrone isomers; monohydroxy bicyclopyrone isomers + monohydroxy bicyclopyrone glycoside (isomers)
	120	Desmethyl monohydroxy bicyclopyrone isomers; monohydroxy bicyclopyrone isomers	None
	270	monohydroxy bicyclopyrone isomers + monohydroxy bicyclopyrone glycoside (isomers)	CSCD656832 + conjugate; CSCD686480
Turnip foliage	60	Monohydroxy bicyclopyrone isomers	None
	270	None	CSCD656832
Turnip tuber	60	Monohydroxy bicyclopyrone isomers	None
Spinach foliage	120	None	bicyclopyrone
	180	bicyclopyrone	bicyclopyrone
-The uptake of overall TRR was the highest in wheat commodities, where residues decreased with increasing PBI. The parent was not detected in wheat and turnip matrices; however, it was a predominant residue in spinach (120 and 180 day PBIs). The parent was extensively metabolized in wheat, in particular in the grain where a significant proportion of the residue was attributed to naturally incorporated radioactivity.A major soil degradation product (CSCD656832) was detected in all wheat commodities, but only at the later rotation intervals.			
Major Metabolic Pathways in Field Corn, Sugarcane Foliage, and Rotational Crops Hydroxylation of the bicyclooctenone ring in at least two positions to produce isomers of monohydroxylated and dihydroxylated bicyclopyrone Cleavage between the bicyclooctenone and pyridine ring systems of bicyclopyrone O-demethylation and successive oxidation of the methoxyethoxymethyl side chain of bicyclopyrone to produce desmethyl, carboxyl , and hydroxyl metabolites followed by conjugation of some metabolites to form their O-glycosides, and several isomers.			

Overall Metabolic Profile in Field Corn, Sugarcane Foliage and Rotational Crops.



FC = Field Corn; SG = Immature Sugarcane Foliage; RotC = Rotational Crops
Red = All three (FC; SG; RotC); Blue = Only FC & RotC; Green = Only FC; Purple = Only RotC

NATURE OF THE RESIDUE IN LAYING HEN						**PMRA #2231738**	
Group	Species	Radiolabel position	No. of animals	Application details		Sampling details	
				Dose/day (mg a.i./kg dry feed/day)	Duration (days)	Commodity	Collection Time
Laying hens (Gallus gallus domesticus)	ISA Brown	[Bicyclooctenone-6,7-14C2] – bicyclopyrone	5/ Radiolabel for a total of 10	22.04	10	Eggs (from ovary and oviduct)	Twice daily
						Excreta	Once daily
		[Pyridine-3-14C] – bicyclopyrone		24.06		Liver, composite muscle, peritoneal fat, skin and subcutaneous fat,	At sacrifice (11 hrs from last dose)

						G.I. tract content	

Analytical Method Overall TRR Identification & Characterization	Combustion/LSC TLC; LC-MS/MS
Extraction Solvents	Acetonitrile:Water (4:1, v/v); Acetonitrile:Water (3:7, v/v); Acetonitrile
Storage Interval at ≤-20°C	Analysis of all samples was conducted within 6 months of necropsy.
Egg plateau	6 to 8 days

Matrices	[Bicyclooctenone-6,7-14C2]		[Pyridine-3-14C]	
	TRRs (ppm), expressed as parent equivalent	% of Administered Dose	TRRs (ppm), expressed as parent equivalents	% of Administered Dose
Excreta	Not reported	75.94	Not reported	76.01
Cage wash	Not reported	2.374	Not reported	3.671
G.I. contents	0.859	0.196	1.511	0.302
Egg yolk (day 8-10)	0.103	0.019	0.104	0.021
Egg white (day 8-10)	0.095	0.078	0.120	0.103
Liver	1.923	0.415	1.906	0.419
Composite muscle	0.086		0.133	
Peritoneal fat	0.191		0.122	
Skin/subcutaneous fat	0.364		0.435	

The majority of the administered dose was excreted (76%) for both radiolabels. The highest residues of bicyclopyrone equivalents were in the liver>skin/subcutaneous fat>peritoneal fat>eggs > composite muscle.

Metabolites identified	Major Metabolites (>10% of the TRRs)	
Radiolabel Position	[Bicyclooctenone-6,7-14C2]	[Pyridine-3-14C]

The parent was the predominant residue in all laying hen matrices. Minor components that were confirmed consisted of hydroxylated, monohydroxylated, desmethyl dihydroxy, and desmethyl monohydroxy metabolites of bicyclopyrone.

Egg yolk (day 8-10)	bicyclopyrone	bicyclopyrone
Egg white (day 8-10)	bicyclopyrone	bicyclopyrone
Liver	bicyclopyrone	bicyclopyrone
Composite muscle	bicyclopyrone	bicyclopyrone
Peritoneal fat	bicyclopyrone	bicyclopyrone
Skin/subcutaneous fat	bicyclopyrone	bicyclopyrone

NATURE OF THE RESIDUE IN LACTATING GOAT				PMRA # 2231742	
Group	Species	Radiolabel position	No. of animals	Application details	
				Dose/day (mg a.i./kg dry feed/day)	Duration (days)
Lactating goat (Capra hircus)	Toggenburg Cross and British Alpine	[Bicyclooctenone -6,7-14C2] – bicyclopyrone	1/radiolabel for a total of 2	34.34	7
		[Pyridine-3-14C] –bicyclopyrone		33.79	

Sampling details	
Matrices	Sampling Times
Milk	Collected twice daily. One milk sample from each animal was centrifuged to separate the cream and the aqueous portions.
Excreta	Collected once daily.
Muscle (loin, hind and forequarter), fat (omental, renal, subcutaneous), liver, kidney, G.I. tract, bile and blood	At sacrifice (11 hrs from last dose)
Analytical Method Overall TRR Identification & Characterization	Combustion/LSC TLC; LC-MS/MS
Extraction Solvents	Acetonitrile:Water (4:1, v/v); Acetonitrile:Water (3:7, v/v); Acetonitrile
Storage Interval at ≤-18°C	Analysis of all samples was conducted within 6 months of necropsy.
Milk plateau	Days 2-4 for both radiolabels (combined AM and PM doses)

Matrices	[Bicyclooctenone-6,7-14C2]-bicyclopyrone		[Pyridine-3-14C]-bicyclopyrone	
	TRRs (ppm), expressed as parent equivalent	% of Administered Dose	TRRs (ppm), expressed as parent equivalent	% of Administered Dose
Urine	Not reported	62.37	Not reported	59.79
Feces	Not reported	6.242	Not reported	6.504
Cage wash	Not reported	13.04	Not reported	19.50
Milk	0.017 (representative sample with highest TRR on day 7 PM)	0.025	0.017 (representative sample with highest TRR on day 3 PM)	0.021
Liver	2.987	0.808 (composite all tissues)	2.750	0.697 (composite all tissues)
Kidney	1.366		1.318	
Composite muscle	0.024		0.025	
Renal fat	0.018		0.013	
Subcutaneous fat	0.024		0.030	

The majority of the radioactivity was excreted via urine (60-62%) with lesser amount in the feces (6.2-6.5%) for both radiolabels. There was low tissue burden. The overall TRR were highest in the liver>kidney>composite muscle>composite fat >milk. Bicyclopyrone and CSAA915194 were the predominant residues in milk and tissues.

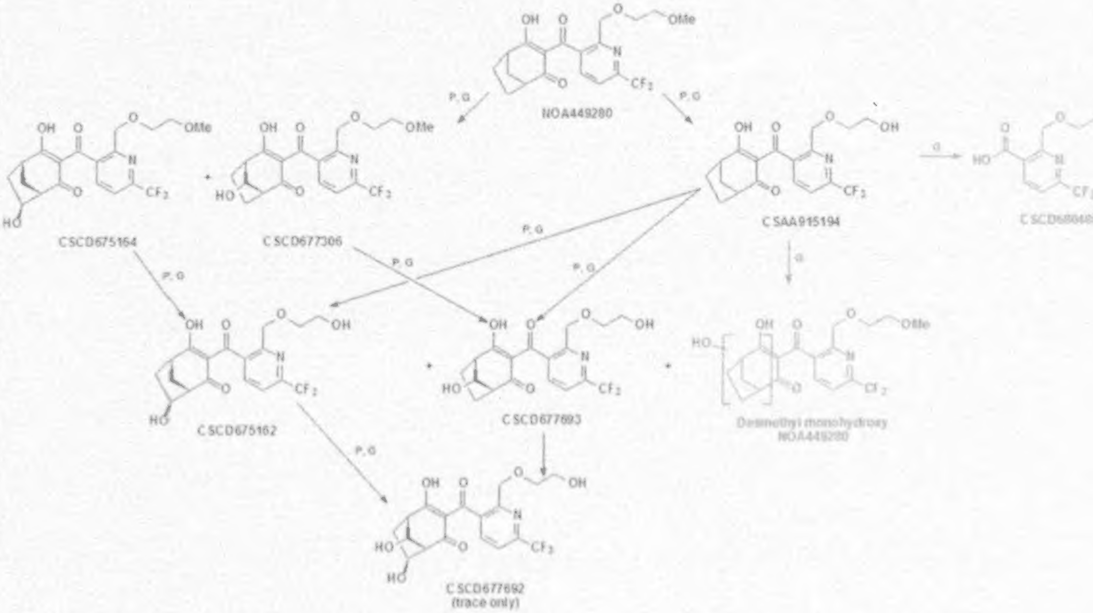
Metabolites identified	Major Metabolites (>10% of the TRRs)	
Radiolabel Position	[Bicyclooctenone-6,7-14C2]	[Pyridine-3-14C]
Minor components were comprised of monohydroxy-, dihydroxy-, and desmethyl monohydroxy metabolites, which were mainly detected in urine.		
Milk (day 3 pm)	bicyclopyrone; CSAA915194	bicyclopyrone; CSAA915194
Liver	bicyclopyrone; CSAA915194	bicyclopyrone; CSAA915194

Liver debris	None	None
Kidney	bicyclopyrone; CSAA915194	bicyclopyrone; CSAA915194
Composite muscle	bicyclopyrone; CSAA915194	bicyclopyrone; CSAA915194
Subcutaneous fat	bicyclopyrone; CSAA915194	bicyclopyrone; CSAA915194
Renal fat	bicyclopyrone; CSAA915194	bicyclopyrone; CSAA915194

Major Metabolic Pathway in Lactating Goat
O-demethylation of the methoxyethoxymethyl side chain of the pyridine ring to form a primary alcohol
Hydroxylation of the bicyclooctenone ring
Cleavage between the bicyclooctenone and pyridine ring systems
Conjugation of metabolites with glucuronic acid (excreta only).

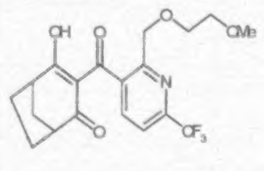
Major Metabolic Pathway in Laying Hen
O-demethylation of the methoxyethoxymethyl side chain of bicyclopyrone to produce the desmethyl metabolites
Hydroxylation of the bicyclooctenone ring to produce isomers of monohydroxylated and dihydroxylated bicyclopyrone

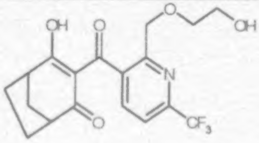
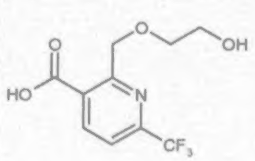
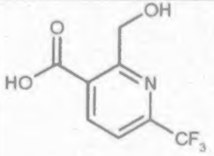
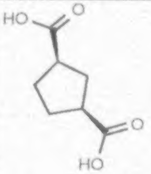
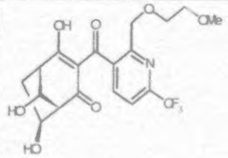
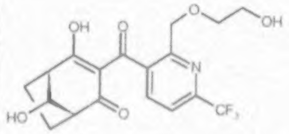
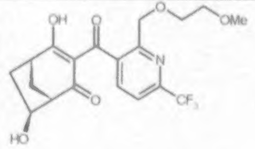
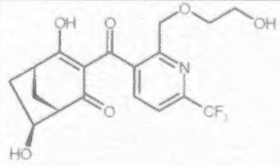
Overall Metabolic Profile in Livestock and Hen.

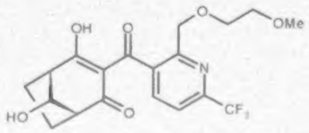
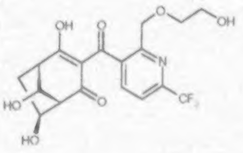
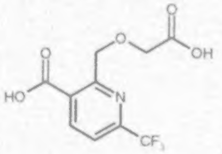
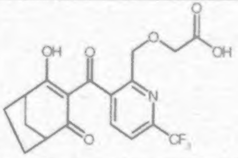
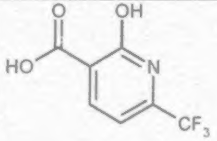
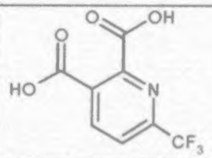
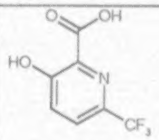


P = Poultry (Laying Hen); G = Lactating Goat
Blue = Poultry and Goat; Purple = Only Goat

Chemical Structure, and Codes of Bicyclopyrone and Metabolites Identified in Metabolism Studies.

Code	Chemical Structure	Found In
Bicyclopyrone (bicyclopyrone) C19H20F3NO5 M = 399.4 gmol-1		Field Corn, Rotational Wheat, Turnips, and Spinach
		Poultry, Goat

CSAA915194 C18H18F3NO5 M = 385.3 gmol-1		Rotational Spinach Poultry, Goat
CSCD686480 C10H10F3NO4 M = 265.2 gmol-1		Sugar Cane, Field corn, Rotational Wheat + glycoside (Sugar Cane, Field Corn, Rotational Wheat) Goat
CSAA806573 C8H6F3NO3 M = 221.1 gmol-1		Field corn, Rotational Wheat + glycoside (Field Corn, Rotational Wheat)
CSAA589691 C7H10O4 M = 158 gmol-1		Field Corn
CSCD677694 C19H20F3NO7 M = 431.4 gmol-1		Sugar Cane, Field Corn, Rotational Wheat
CSCD677693 C18H18F3NO6 M = 401.3 gmol-1		Sugar Cane, Field Corn, Rotational Wheat and Turnips + glycoside (Sugar Cane) Poultry, Goat
CSCD675164 C19H20F3NO6 M = 415.4 gmol-1		Field Corn, Rotational Wheat and Turnips + glycoside (Sugarcane, Rotational Wheat) Poultry, Goat
CSCD675162 C18H18F3NO6 M = 401.3 gmol-1		Sugar Cane, Field Corn, Rotational Wheat and Turnips + glycoside (Field Corn, Rotational Wheat)

		Poultry, Goat
CSCD677306 $C_{19}H_{20}F_3NO_6$ M = 415.4 gmol-1		Sugar Cane, Field Corn, Rotational Wheat and Turnips + glycoside (Sugar Cane, Rotational Wheat)
		Poultry, Goat
CSCD677692 $C_{18}H_{18}F_3NO_7$ M = 417.3 gmol-1		Sugar Cane, Field Corn, Rotational Wheat
		Poultry, Goat
CSCD686481 $C_{10}H_8F_3NO_5$ M = 279.2 gmol-1		Sugar Cane, Field Corn, Rotational Wheat
CSCD642512 $C_{18}H_{16}F_3NO_6$ M = 399.3 gmol-1		Field Corn, Rotational Wheat
CSAA757083 $C_7H_4F_3NO_3$ M = 207.1 gmol-1		Rotational Wheat
CSCC163768 $C_8H_4F_3NO_4$ M = 207.1 gmol-1		Rotational Wheat
CSCD656832 $C_7H_4F_3NO_3$ M = 207.1 gmol-1		Rotational Wheat and Turnips + conjugate (Field Corn, Rotational Wheat and Turnips)

FREEZER STORAGE STABILITY – PLANT MATRICES (RAC)	**PMRA # 2231727**

A storage stability study was conducted by fortifying several plant RACs individually at 0.2 ppm with bicyclopyrone and the analyte SYN503780 following storage at ≤-20°C. Residues of bicyclopyrone and SYN503780 were determined at intervals of 0, 3, 6, 12, 18 and 24 months using the analyte-specific method GRM030.03A. There was no evidence of residue dissipation over the intervals tested. Since no decline in the components of the residue definition was observed in 5 RAC commodity categories, the demonstrated duration of stability in all processed commodities would be covered by the demonstrated duration of stability in the RACs. The metabolite CSCD686480, which is part of the residue definition for plant matrices, was not addressed in this study. Re-analysis of field corn samples from the metabolism study after 16 months of storage, and spring wheat samples from the confined rotational crop study after 16-18 months of storage indicated no significant change in the radiocomponent profiles (which included CSCD686480) over these periods of time. Concurrent storage stability data submitted within the sugarcane crop field trial study also indicated that CSCD686480 was stable in sugarcane cane for up to 22.3 months of frozen storage. These intervals cover the storage intervals of samples from the crop field trial, processing and field accumulation studies.

Plant matrices (Raw Agricultural Commodities):

Commodity categories	Representative commodities	Demonstrated duration of stability
High-starch content	Corn (grain, straw), potato tuber	Residues of bicyclopyrone and SYN503780 (analysed by Method GRM030.03A) are stable at ≤-20°C for 24 months.
High-water content	Spinach leaf	
High-oil content	Soybean seeds	
High-protein content	Lentil seed	
High-acid content	Lemon fruit	

FREEZER STORAGE STABILITY – ANIMAL MATRICES	PMRA # 2294395

Bovine muscle, liver, fat, milk; poultry eggs: A storage stability study was conducted by fortifying bovine tissues and eggs individually at 0.1 ppm with bicyclopyrone, SYN503780 and CSCD686480. Samples were stored in a sealed container at ≤-10°C. Residues of bicyclopyrone, SYN503780 and CSCD686480 were determined at intervals of 0, 1, 6, 14 and 16 months using the common moiety enforcement method GRM030.08A. There was no evidence of residue dissipation over the intervals tested.

CROP FIELD TRIALS ON CORN, SUGARCANE	PMRA # 2376141, 2231751

	CORN (Field, sweet, popcorn) (Domestic Commodity)	SUGARCANE (Imported Commodity)
No. of trials	29 (US)	8 (Australia)
Trial locations	Conducted in NAFTA growing regions (1, 2, 3, 5, 7,10, 11, 12)	Treated in representative regions of Australia
Formulation type	200 g a.i./L soluble concentrate	200 g a.i./L emulsifiable concentrate
Application type/rate	1 over the top post-emergent spray (spray volumes of 140-271 L/ha)	2 foliar applications for total rates of either 300 or 600 g a.i./ha (spray volumes of 384-413 L/ha)
Analytical Method	Common Moiety method GRM030.05A	
Adjuvant use	Crop oil concentrate, or non-ionic surfactant (NIS)	Agral (NIS) @0.25%
Residue decline	Not conducted	Not conducted
X-fold GAP	1-fold (49-55 g a.i./ha)	1-fold (300 g a.i./ha), 2-fold (600 g a.i./ha)

Storage stability		Maximum of 17.8 months from harvest to analysis (≤ -10 °C).				Maximum of 26 months from harvest to analysis (≤ -18 °C).					
Crop/ Fractions	Analyte	Total Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)[1]							
				n	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Sweet Corn: Proposed Use = 50 g a.i./ha season, 45 day PHI (forage); 45-50 day PHI (K+CWHR).											
Forage	Bicyclopyrone (and its structurally related metabolites)[2]	49-55	34-54	12*	<0.02	0.280	<0.02	0.229	0.115	0.111	0.067
Stover		49-55	48-96	7	<0.02	0.373	0.026	0.291	0.077	0.143	0.118
K+CWHR		49-55	34-54	12*	<0.02	0.023	<0.02	0.023	0.02	0.020	0.001
*2 sweet corn trials were not included as they were conducted at PHIs that were outside 25% of GAP.											
Field Corn: Proposed Use = 50 g a.i./ha/season, 45-90 day PHI (forage); Maturity (field corn grain and stover).											
Forage	Bicyclopyrone (and its structurally related metabolites)[2]	50-52	39-47	17	<0.02	0.229	<0.02	0.178	0.097	0.102	0.044
Stover		50-52	80-113	17	<0.02	0.277	<0.02	0.270	0.052	0.075	0.064
Grain		50-52	80-113	17	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	-
Popcorn											
Stover	Bicyclopyrone (and its structurally related metabolites)[2]	50	98-100	2	<0.02	0.050	0.024	0.045	0.035	0.035	0.015
Grain		50	98-100	2	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	-
Sugarcane: Proposed Use = 150-300 g a.i./ha/season, No PHI required when used as directed on the label											
Sugarcane Cane	Bicyclopyrone (and its structurally related metabolites)[2]	300	28	8	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	-
		600	28	8	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	-
[1] Values based on per-trial averages. For computation of the LAFT, HAFT, median, mean and standard deviation, values < LOQ are assumed to be at the LOQ. [2] The residue values are determined as the sum of common moieties SYN503780 (expressed as bicyclopyrone equivalents) and CSCD686480 (expressed as CSAA915194 equivalents).											
RESIDUE DATA IN ROTATIONAL CROPS									PMRA #2231571, 2231766		
STUDY 1 - EXPERIMENTAL DESIGN											
No. of trials (regions)		9 in US (NAFTA regions 2, 4, 5, and 6)									
Formulation type		250 g active ingredient (a.i.)/L Emulsifiable concentrate									

Application type/rate	One soil surface broadcast application to the bare soil at 202 - 213 g a.i./ha (spray volumes of 175-225 L/ha).
Analytical Method	Common Moiety method GRM030.05A
Storage stability (<-10 °C)	Maximum of 9.5 months from sampling to analysis.

Crop/ Crop group	Variety	No of Trials	PBI	Growth stage at harvest	Harvested RAC
Spinach/ leafy vegetable	Melody Siena F1	2	90	At maturity – crop failure at 1 site	Mature leaves
	Hybrid #7	1	150	At maturity – crop failure at 2 sites	
	Siena F1	1	180	At maturity	
	Hybrid #7	2	270	Not harvested – crop failure	
Radish (root and tuber vegetable)	Cheriette	3	90	At maturity	Mature root and tops
	Cherry bell	2	150	At maturity – crop failure at one site	
	Cherry bell	3	270	At maturity	
Wheat (small grain)	AGS 2000 (winter wheat)	3	90	Fall forage – 60 days after planting Spring forage – 6-8 inch stem elongation Wheat hay – boot to soft dough stage Wheat straw and grain – at maturity	Forage, hay, wheat, straw
	BWW-1005 (Spring wheat)	3	150		
	BWW-1005 (Spring wheat)	3	270		

Crop	Analyte	Total Rate (g a.i./ha)	PBI (day)	Residue Levels (ppm)[1]							
				n	Min.	Max.	LAFT	HAFT	Median	Mean	SD
STUDY 1: Spinach, Radish, Winter Wheat and Spring Wheat											
Spinach	Bicyclopyrone (and its structurally related metabolites)^2	202-213	90	4	<0.020	0.023	<0.020	0.022	0.021	0.021	-
Radish Tops				6	<0.020	0.035	<0.020	0.030	0.021	0.024	0.006
Radish Roots				6	<0.020	<0.020	<0.020	<0.020	<0.020	<0.020	-
Wheat (forage, hay, straw, & grain)				6	<0.020	<0.020	<0.020	<0.020	<0.020	<0.020	-
Spinach		202-213	150	2	<0.020	<0.020	<0.020	<0.020	-	-	-
Radish Tops				4	<0.020	0.026	<0.020	0.024	0.022	0.022	-
Radish Roots				4	<0.020	<0.020	<0.020	<0.020	<0.020	<0.020	-

Wheat (forage, hay, straw, & grain)				6	<0.020	<0.020	<0.020	<0.020	<0.020	<0.020	-
Spinach		202-213	180	2	<0.020	<0.020	<0.020	<0.020	-	-	-
Radish Tops		202-213	270	6	<0.020	<0.020	<0.020	<0.020	<0.020	<0.020	-
Radish Roots				6	<0.020	<0.020	<0.020	<0.020	<0.020	<0.020	-
Wheat (forage, hay, straw, & grain)				6	<0.020	<0.020	<0.020	<0.020	<0.020	<0.020	-

[1] Values based on per-trial averages. For computation of the LAFT, HAFT, median, mean and standard deviation, values < LOQ are assumed to be at the LOQ.

[2] The residue values are determined as the sum of common moieties SYN503780 (expressed as bicyclopyrone equivalents) and CSCD686480 (expressed as CSAA915194 equivalents).

STUDY 2 - EXPERIMENTAL DESIGN	
No. of trials (regions)	20 in US (NAFTA growing regions (2, 4, 5, 6, 7, 8, 11)
Formulation type	250 g active ingredient (a.i.)/L Emulsifiable concentrate
Application type/rate	One soil surface broadcast application to the bare soil at 202 g a.i./ha (4-fold GAP) with spray volumes of 112-560 L/ha
Analytical Method	Common moiety method GRM030.05A
Storage stability (<-10 °C)	Maximum of 13.0 months from sampling to analysis.

Crop	Variety	No of Trials	PBI (day)	Growth stage at harvest	Harvested RAC
Winter Wheat (regions 2,4,5,6,8,11)	Coker 9663, Terral LA841, Arlin, Santa Fe, 733, Briggs, Mit, Bill Brown, Yuma, Jagalene, TAM105, Fannin, Deliver, Stephens	15	88-93	Fall forage = 45 d after planting Hay = early flower (boot) to soft dough stage Grain and straw = Maturity	Fall Forage, hay, straw, grain
Spring Wheat (region 7)	CA907-816W, Agawam,WPB Nick, Divide, Diamond	5	271-272	Spring forage = 6 to 8 inch stage to stem elongation Hay = early flower (boot) to soft dough stage Grain and straw = Maturity	Spring forage, hay, straw, grain

Crop	Analyte (ppm)	Total Rate (g a.i./ha)	PBI (days)	Residue Levels (ppm)1							
				n	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Winter Wheat Fall Forage	Bicyclopyrone (and its structurally related metabolites)[2]	202	88-93	15	<0.020	0.038	<0.020	0.0345	<0.02	0.021	0.004
Winter wheat hay, straw, grain		202	88-93	15	<0.020	<0.020	<0.020	<0.020	<0.020	<0.020	-
			271-272	15	<0.020	<0.020	<0.020	<0.020	<0.020	<0.020	-
Spring Wheat forage, hay, straw and grain		202	88-91	5	<0.020	<0.020	<0.020	<0.020	<0.020	<0.020	-
			271-272	5	<0.020	<0.020	<0.020	<0.020	<0.020	<0.020	-

[1] Values based on per-trial averages. For computation of the LAFT, HAFT, median, mean and standard deviation, values < LOQ are assumed to be at the LOQ.

[2] The residue values are determined as the sum of common moieties SYN503780 (expressed as bicyclopyrone equivalents) and CSCD686480 (expressed as CSAA915194 equivalents).

PROCESSED FOOD AND FEED – FIELD CORN, SUGARCANE	PMRA #2231569, 2231755
Field Corn	
Test Site	Two trials in NAFTA Growing Region 5.
Treatment	Post emergence over the top broadcast foliar applications
Rate	Trt 1: 197-202 g a.i./ha (4-fold GAP) Trt 2: 992-1006 g a.i./ha (20-fold GAP)
End-use product/formulation	250 g a.i./L emulsifiable concentrate formulation
Analytical Method	Common Moiety method GRM030.05A The residue values are determined as the sum of common moieties SYN503780 (expressed as bicyclopyrone equivalents) and CSCD686480 (expressed as CSAA915194 equivalents).
Preharvest interval	111-118 days (3.7-3.9 months)
Processed Commodities: AGF, flour, germ, meal, hulls, oil, grits, gluten and starch	Residues of the common moieties SYN503780 and CSCD686480 were all <LOQ (<0.01 ppm) in field corn grain and the processed commodities of AGF, flour, germ, meal, hulls, oil, grits, gluten and starch. Therefore, there was no concentration of residues in any of the field corn processed fractions.
Sugarcane	
Test Site	Two trials in Brazil.
Treatment	Pre-emergence spray application

Rate	900 g a.i./ha (3-fold maximum GAP) or 1500 g a.i./ha (5-fold maximum GAP)
end-use product/formulation	200 g a.i./L soluble concentrate formulation
Analytical method	Data gathering methods POPIT MET116 and POPIT MET 117
Preharvest interval	244 days (8.0 months)
Processed Commodities: Sugar, molasses, bagasse	Residues of the common moieties SYN503780 and CSCD686480 were <LOQ (<0.01 ppm) in all sugarcane stalk samples at both the 3-fold and 5-fold maximum GAP application rates. Therefore, stalks were not processed into fractions of sugar, molasses or bagasse.
LIVESTOCK FEEDING – Dairy cattle	PMRA #2231762

Species	Age/Weight at Dosing	Average Feed Consumption	# Animals	Application details		Sampling details	
				Rate (ppm feed) via gelatin capsule	Duration (days)	Commodity	Collection Time
Lactating Dairy Cow (Holstein)	3-5years old/ 451-632 kg	15-21 kg/animal/ day (dry weight)	Group 1: 1 Group 2: 3 Group 3: 3 Group 4: 3	Group 1: 0 Group 2: 0.15 Group 3: 0.9 Group 4: 3.0	28	Milk	Collected in the evening and following morning prior to dosing.
						Liver, kidney, fat, and muscle	At sacrifice (22-24 hrs after last dose)
Analytical Method			Common Moiety Method GRM030.08A				

Matrix	Analyte (ppm)	Feeding Level ppm	Sampling Day*	Residue Levels (ppm)[1]					
				n	Min.	Max.	Median	Mean	SD
Milk	Bicyclopyrone (and its structurally related metabolites)[2]	3.0	-1	3	<0.020	<0.020	<0.020	<0.020	-
			1	3	<0.020	<0.020	<0.020	<0.020	-
			3	3	<0.020	<0.020	<0.020	<0.020	-
			7	3	<0.020	<0.020	<0.020	<0.020	-
			10	3	<0.020	<0.020	<0.020	<0.020	-
			14	3	<0.020	<0.020	<0.020	<0.020	-
			17	3	<0.020	<0.020	<0.020	<0.020	-
			21	3	<0.020	<0.020	<0.020	<0.020	-
			24	3	<0.020	<0.020	<0.020	<0.020	-
			28	3	<0.020	<0.020	<0.020	<0.020	-
Fat		3.0	28	3	<0.020	<0.020	<0.020	<0.020	-
Muscle		3.0	28	3	<0.020	<0.020	<0.020	<0.020	-

Liver		0.15	28	3	0.764	1.014	0.935	0.904	0.128
		0.9		3	1.312	1.792	1.664	1.589	0.249
		3.0		3	0.385	2.262	1.458	1.368	0.942
Kidney		0.15	28	3	0.247	0.339	0.294	0.293	0.046
		0.9		3	0.294	0.446	0.358	0.366	0.076
		3.0		3	0.349	0.397	0.352	0.366	0.027

[1] For computation of the median, mean and standard deviation, values < LOQ are assumed to be at the LOQ.

[2] The residue values are determined as the sum of common moieties SYN503780 (expressed as bicyclopyrone equivalents) and CSCD686480 (expressed as CSAA915194 equivalents).

*Sampling day 28 = Day of sacrifice

Overall Assessment of Lactating Cow Feeding Study

For milk, muscle and fat, the sum of residues from the common moieties SYN503780 (expressed as bicyclopyrone equivalents) and CSCD686480 (expressed as CSAA915194 equivalents) were <LOQ (0.02 ppm) at the highest feeding level, so no analysis of samples at the lower feeding levels was conducted. Residues were dose dependent in liver, but not in kidney. No depuration study was conducted.

A storage stability study was conducted concurrently by fortifying dairy cow matrices (milk, fat, liver, kidney and muscle) at 0.01 ppm with SYN503780 and CSCD686480. Samples were stored at <-10°C. Residues of SYN503780 and CSCD686480 were determined at an interval of 12.8 months, and there was no evidence of residue dissipation over the interval tested.

Dietary Burden and Anticipated Residues in Meat, Meat by-products, Milk and Eggs for Enforcement

The livestock feedstuff items associated with the proposed uses in Canada include corn (field, sweet), and winter wheat (90 day PBI, as a rotational crop).

Matrix Type	Dietary Burden (ppm)
Beef Cattle	0.09
Dairy Cattle	0.22
Poultry	0.02
Swine	0.02

Commodity	Feeding Level (ppm)	Highest Residues (ppm)	Dietary Burden (ppm)		Anticipated Residues (ppm)	
			MRL	DEA	MRL	DEA
Cattle						
Milk	3.0	<0.02	0.22	0.22	0.0015	0.0015
Muscle	3.0	<0.02		0.09	0.0015	0.0006
Fat1	3.0	<0.02			0.0015	0.0006
Liver	0.15	1.014			1.2	0.69
	0.9	1.792				
	3.0	2.262				

Kidney	0.15	0.339			0.37	0.31
	0.9	0.446				
	3.0	0.397				
Swine						
Muscle	3.0	<0.02	0.02		0.00013	
Fat1	3.0	<0.02			0.00013	
Liver	0.15	1.014			0.2	
	0.9	1.792				
	3.0	2.262				
Kidney	0.15	0.339			0.15	
	0.9	0.446				
	3.0	0.397				

[1] Equal amounts of perirenal fat, mesenteric fat, and subcutaneous fat.

LIVESTOCK FEEDING – Laying hens	PMRA # 2231738

No poultry feeding study was submitted, but a hen metabolism study was conducted at 22-24 ppm in the feed (1100 to1200-fold the estimated poultry dietary burden of 0.02 ppm) with two radiolabels, which can be used to determine the anticipated residues in poultry matrices. As corn (primary crop) and wheat (rotational crop) can be fed to poultry, anticipated residues were determined by using the residue to feed (R/F) ratio multiplied by the estimated poultry dietary burden. The residue values used were the highest of the 2 radiolabels examined for each matrix at the corresponding feeding level. The anticipated residues for all poultry matrices were less than the method LOQ of 0.01 ppm per analyte.

Commodity	Feeding Level (ppm)	Highest Residues (ppm)	Anticipated Residues (ppm)
Egg yolk	24 (pyridinyl label)	0.082	0.00007
Egg white	24 (pyridinyl label)	0.119	0.000099
Liver	24 (pyridinyl label)	1.514	0.00126
Composite muscle	24 (pyridinyl label)	0.112	0.000093
Peritoneal fat	22 (bicyclooctenone label)	0.174	0.00016
Skin and subcutanous fat	24 (pyridinyl label)	0.461	0.00038

Table 6 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT/RISK ASSESSMENT Primary crops (field corn, sugarcane) Rotational crops (wheat, turnips, spinach)	Bicyclopyrone and its structurally related metabolites determined as the common moieties SYN503780 and CSCD686480 (expressed as bicyclopyrone equivalents).
Rationale for Residue Definition Selection in Plants	The proposed residue definition for enforcement and risk assessment in crops is bicyclopyrone and its structurally related metabolites determined as the common moieties SYN503780 and CSCD686480 (expressed as bicyclopyrone equivalents). Bicyclopyrone was not detected in any of the primary crops, and only in the spinach from the confined rotational crop. Bicyclopyrone and all of its major metabolites identified in the metabolism studies (primary and rotational crop and livestock) were converted to the common moieties SYN503780 and CSCD686480 by the proposed enforcement methods, with the following exceptions: CSAA589691 in corn grain; and CSCD656832 in rotational crops, beginning at the 120-day PBI with increased amounts at the 270-day PBI. CSAA589691 was <0.02 ppm in field corn grain, with comparable residues found in the untreated samples, therefore this metabolite can be excluded from the residue definition. In rotational crops, CSCD656832 did not comprise a significant portion of the total residue until the 270-day PBI. Therefore, the portion of the residue converted to the common moieties SYN503780 and CSCD686480 is adequate to serve as a marker in all rotational crops, except for 270-day turnip foliage (71% of the TRR, 0.012 ppm CSCD656832). Based on the low residue level observed (0.012 ppm) and the degree of exaggeration (4-fold) from the confined rotational crop study, it is unlikely that quantifiable residues of the metabolite CSCD656832 would be found under field accumulation condition. Therefore, CSCD656832 can be excluded as a part of the residue definition in rotational crops.
METABOLIC PROFILE IN DIVERSE CROPS	Qualitatively, the metabolic profile for bicyclopyrone in primary crops (field corn and sugarcane) and rotational crops were similar. Quantitatively, metabolites resulting from bridge cleavage were more prevalent in the rotational crops than in the primary crops as they were formed to a larger extent at the later plantback intervals.

PLANT STUDIES	
ANIMAL STUDIES	
ANIMALS	Ruminant and Poultry
RESIDUE DEFINITION FOR ENFORCEMENT/RISK ASSESSMENT	Bicyclopyrone and its structurally related metabolites determined as the common moieties SYN503780 and CSCD686480 (expressed as bicyclopyrone equivalents).
Rationale for Residue Definition Selection in Livestock	The proposed residue definition for enforcement and risk assessment in livestock is bicyclopyrone and its structurally related metabolites determined as the common moieties SYN503780 and CSCD686480 (expressed as bicyclopyrone equivalents). Bicyclopyrone was detected in eggs and all laying hen tissues. Bicyclopyrone and CSAA915194 were detected in milk and all lactating goat tissues. Therefore, the portion of the residue converted to the common moieties SYN503780 and CSCD686480 is adequate to serve as a marker in all livestock matrices.
METABOLIC PROFILE IN ANIMALS (goat, hen)	The profile is similar in animals.
FAT SOLUBLE RESIDUE	No

DIETARY RISK FROM FOOD AND WATER			
Non-cancer dietary exposure analysis ADI = 0.001 mg/kg bw/day Estimated chronic drinking water concentration (Level 2) = 17 µg/L	POPULATION	REFINED ESTIMATED RISK 95% PERCENTILE % of ACCEPTABLE DAILY INTAKE (ADI)	
		Food Alone	Food and Water
	General population	4.9	40.5
	All Infants	8.0	99.8
	Children 1–2 years	15.3	66.6
	Children 3 to 5 years	12.8	56.0
	Children 6–12 years	8.8	40.0
	Youth 13–19 years	5.2	31.2
	Adults 20–49 years	3.8	39.4
	Adults 50-99 years	2.8	37.9
ARfD = 0.001 mg/kg bw (females 13-49 years old) ARfD = 2.0 mg/kg bw (total population)	POPULATION	REFINED ESTIMATED RISK 95th PERCENTILE % of ARfD	
		Food Alone	Food and Water
	General population	0.01	0.05
	All infants	0.01	0.15
	Children 1–2 years	0.02	0.08

PLANT STUDIES			
Estimated acute drinking water concentration (level 2) = 17 µg/L	Children 3 to 5 years	0.01	0.06
	Children 6–12 years	0.01	0.05
	Males 13–19 years	0.01	0.04
	Males 20–49 years	0.00	0.04
	Adults 50-99 years	0.00	0.04
	Females 13-49 years	9.41	96.6

Table 7 Fate and Behaviour in the Environment

Study Type	**Study Endpoints/Information**	**COMMENTS**	**PMRA Number**
Physical and Chemical Properties of TGAI			
Vapour pressure at 20°C	$< 5 \cdot 10^{-6}$ Pa (pure substance)	Relatively non-volatile under field conditions	2231454
Henry's law constant at 25°C	$< 1.7 \cdot 10^{-6}$ Pa m³/mol $< 1.7 \times 10^{-11}$ atm m³/mol (pH 7.2) $H = 6.89 \times 10^{-10}$	Not expected to volatilise from moist soil or water surfaces	
Solubility in water at 20°C	pH 4.9 = 38 g/L pH 7.2 = 119 g/L pH 9.2 = 119 g/L	Soluble to very soluble in water, depending on pH level, indicates potential for leaching behaviour	
n-Octanol/water partition coefficient at 25°C (Log K_{ow})	pH 5 = 0.25 pH 7 = -1.2 pH 9 = -1.9	Not expected to bioaccumulate	
Dissociation constant (pK_a) at 20°C	3.06	Will exist as an anion at environmentally relevant pH levels, indicates potential for leaching behaviour	

Study Type	Study Endpoints/Information	COMMENTS	PMRA Number
Abiotic Transformation			
Hydrolysis (TGAI)	hydrolytically stable at pH values of 4, 5, 7, and 9 at 25 °C	Stable to hydrolysis, indicates potential for leaching behaviour	2440945
Photolysis in water (TGAI)	Buffer pH 5, half-life 11.1 days Buffer pH 7, half-life 50.1 days Natural water, half-life 74.8 days	indicates potential for leaching behaviour	2440944
Photolysis on soil (TGAI)	**Nebraska, Silty clay loam soil** Obs. DT50 *ca.* 6 days; obs. DT90>15 days; calculated half-life = 6.1 days (SFO, C_0 = 96.3 k = 0.113), Env. Half-life = 13.3 days **Iowa, USA, Sandy clay loam** Obs. DT50 *ca.* 3 days; obs. DT90: 6-15 days; calculated half-life = 2.5 days (SFO, C_0 = 94.9 k = 0.276), Env. Half-life = 4.4 days **Georgia, Loamy sand soil** Obs. DT50 *ca.* 1 day; obs. DT90>15 days; calculated half-life = 2.1 days (SFO, C_0 = 87 k = 0.331), Env. Half-life = 5.2 days *Environmental half-life determined using the equation (Ln 2) ÷ [(Ln 2/irradiated half-life) - (Ln 2 dark control half-life)] to determine phototransformation half-lives (6.9, 2.6 and 2.2 days), then multiplying by two to correct for continuous irradiation.*		2440942
Biotransformation in water			
Aerobic biotransformation in water (TGAI)	**Switzerland river water:sandy loam sediment (irradiated, 20°C, water pH 7.9, sediment pH 7.3)** Calculated half-life = 7.5 days (SFO; C_0 = 98.1, k = 0.0924, S_c = 320, S_{SFO} = 311) Obs. DT50: *ca.* 7.5 Major transformation products CSCC163768[2] (43.4%, 29 days) CSAA456156[2] (20.6%, 29 days) Unextracted residues (pyridine label 17.3%, bicyclooctenone label 63.2%,	Non-persistent	2442543

Study Type	**Study Endpoints/Information**	**COMMENTS**	**PMRA Number**
	29 days) **Switzerland pond water:silt loam sediment system (irradiated, 20°C, water pH 7.5, sediment pH 7.1)** Calculated half-life = 7.4 days (SFO; C_0 = 96.3, k = 0.0937, S_c = 193, S_{SFO} = 171) Obs. DT50: *ca*. 7.5 Major transformation products CSCC163768[2] (50.1%, 16 days) CSAA456156[2] (19.7%, 29 days) Unextracted residues (pyridine label 22.6%, bicyclooctenone label 61.7%, 29 days)		
Anaerobic biotransformation in water (TGAI)	**Switzerland river water:sandy loam sediment** (20°C, water pH 8.0, sediment pH 7.2) Observed DT50>105 days, Calculated half-life = 681 (C_0 = 97.4, k = 0.00102, Sc = 61.6, S_{SFO} = 52 (SFO)) **Switzerland pond water:silt loam sediment** (20°C, water pH 7.76, sediment pH 6.9) Observed DT50>105 days, Calculated half-life = 393 days (C_0 = 91.3, k = 0.00176, Sc = 323, S_{SFO} = 284 (SFO))	persistent	2441387
Anaerobic biotransformation in water (TGAI)	**Switzerland river water:sandy loam sediment** (20°C, water pH 8.0, sediment pH 7.2) Observed DT50>105 days, Calculated half-life = 661 days (C0 = 97.2, k = 0.00105, Sc = 58.8, S_{SFO} = 50.7, (SFO)) **Switzerland pond water:silt loam sediment system** (20°C, water pH 7.76, sediment pH 6.9) Observed DT50>105 days, Calculated half-life = 466 (C_0 = 90.7, k = 0.00149, Sc = 347, S_{SFO} = 297 (SFO))	persistent	2441387
Biotransformation in soil			
Aerobic Soil biotransformation at 20°C	**Switzerland, Loam soil** Obs. DT50 *ca.* 21 days; obs. calculated half-life = 19.8 days (SFO, C_0 = 100 k = 0.035),	Slightly persistent	2440943

Study Type	Study Endpoints/Information	COMMENTS	PMRA Number
(TGAI)			
Aerobic Soil biotransformation at 20°C (TGAI)	**Iowa, Sandy clay loam soil** Obs. DT50 *ca* 50 days; Calculated half-life = 53.5 days (IORE;C_0 = 98.2, N = 1.34, k = 0.00312) **Switzerland, Gartenacker, Loam soil** Obs. DT50 *ca* 21 days, Calculated half-life = 21.8 days (IORE, C_0 = 100, N = 0.769, k = 0.0851) **UK, 18 Acres, Sandy clay loam soil** Obs. DT50>120, Calculated half-life = 266 days (DFOP, C_0 = 96.8, f = 0.302, k_0 = 0.0496, k_1 = 0.00125) **France, Marsillargues, Silty clay soil** Obs. DT50 *ca* 79 days, Calculated half-life = 89 days (SFO, C_0 = 97.4, k = 0.0779) **Nebraska, Silt loam soil** Obs. DT50 *ca* 79, Calculated half-life = 68.4 days (SFO, C_0 = 101, k = 0.0101)	Slightly to moderately persistent	2440937 2440939
Aerobic Soil biotransformation at 20°C (TGAI)	**Georgia, Sandy loam soil** Obs. DT50 *ca* 365 days , Calculated half-life = 350 days (DFOP, C_0 = 99.8, f = 0.182, k_0 = 0.0457, k_1 = 0.00141) **Illinois, Silty clay loam soil** Obs. DT50 >120 days, Calculated half-life = 157 days (DFOP, C_0 = 96.4, f = 0.0659, k_0 = 0.236, k_1 = 0.00397) **North Carolina Loamy sand soil** Obs. DT50 *ca* >120 days, Calculated half-life = 331 days (SFO, C_0 = 95.7, k = 0.00209) **Minnesota, Clay loam soil** Obs. DT50 *ca* 120 days, Calculated half-life = 110 days (IORE, C_0 = 100, N = 1.87, k = 0.000159) **Iowa, Sandy loam soil** Obs. DT50 >120 days, Calculated half-life = 335 days (SFO, C0 = 93.7, k = 0.00207) **Michigan, Loamy sand soil**	Moderately persistent to persistent	2440941

Study Type	**Study Endpoints/Information**	**COMMENTS**	**PMRA Number**
	Obs. DT50>120 days, Calculated half-life = 141 days (SFO, C_0 = 91.4, k = 0.00491) **Ohio, Loam soil** Obs. DT50 *ca* 50 days, Calculated half-life = 59.1 days (SFO, C_0 = 97.7, k = 0.0117)		
Anaerobic Soil biotransformation at 20°C (TGAI)	**UK, 18 Acres, Sandy clay loam** Obs. DT50 >119 days, Calculated half-life: Bicyclopyrone was stable during the anaerobic phase of the experiment.	persistent	2441352
Aerobic Soil biotransformation at 20°C **(CSAA806573** - soil metabolite)	**Switzerland, Gartenacker, Loam soil** Obs. DT50 = 0 – 1 day, half-life not calculated as CSAA806563 was only 5.2-6.2% AR at 1 day (first posttreatment sampling interval) **UK, 18 Acres, sandy clay loam** Obs. DT50 = 0 – 1 day, half-life not calculated as CSAA806563 was only 3.4-5.9% AR at 1 day (first posttreatment sampling interval) **France, Marsillargues, Silty clay soil** Obs. DT50 = 0 – 1 day, Calculated half-life = 0.38 days (SFO, C_0 = 87.2, k = 1.84)	Non-persistent	2440927
Aerobic Soil biotransformation at 20°C **(SYN503780** - soil metabolite)	**Switzerland, Gartenacker, Loam soil** Obs. DT50 = 3 – 7 days, calculated half-life = 4.73 days (IORE; C_0 = 95.8, N = 0.611, k = 0.758) **UK, 18 Acres, sandy clay loam** Obs. DT50 = 3 – 7 days, calculated half-life = 5.23 days (SFO; C_0 = 94.9, N = 0.133) **France, Marsillargues, Silty clay soil** Obs. DT50 *ca* 79 days, Calculated half-life = 0.38 days (IORE, C_0 = 97.4, N = 0.739, k = 0.208)	Non-persistent	2440931
Mobility			
Adsorption in soil (TGAI)	**18 Acres Sandy clay loam,(2.9% OC, pH 5.7)** K_d=1.33-4.00 K_{oc}=48 ± 0.8 K_f=1.34 ± 1.0 K_{foc} = 46 ± 35.6 1/n = 0.86 ± 0.0 **Iowa Sandy clay loam,(1.4% OC, pH 6.8)**	Very highly mobile, indicates potential for leaching behaviour	2441353

Study Type	Study Endpoints/Information	COMMENTS	PMRA Number
	K_d=0.23-0.43 K_{oc}= 17 ± 0.2 K_f= 0.25 ± 1.0 K_{foc} = 18 ± 72.6 1/n = 0.92 ± 0.0 **Gartenacker Loam, (2.1% OC, pH 7.0)** K_d=0.18-0.57 K_{oc}= 9 ± 0.2 K_f= 0.20 ± 1.0 K_{foc} = 10 ± 49.1 1/n = 0.85 ± 0.0 **Marsillargues Silty clay, (1.0% OC, pH 7.7)** K_d=0.12-0.27 K_{oc}=12 ± 0.2 K_f=0.14 ± 1.0 K_{foc} = 14 ± 102.2 1/n = 0.90 ± 0.0 **Nebraska Silt loam, (1.6% OC, pH 6.9)** K_d=0.21-0.39 K_{oc}=14 ± 0.2 K_f=1.39 ± 1.1 K_{foc} = 87 ± 65.9 1/n = 0.89 ± 0.0		
Adsorption in soil (TGAI)	**Georgia sandy loam, (0.6% OC, pH 5.8)** K_d= 0.19-0.43 K_{oc}= 34 ± 1.5 K_f= 0.24 ± 1.0 K_{foc} = 39 ± 173.7 1/n = 0.85 ± 0.0 **Illinois Silty clay loam (2.4%OC, pH 5.9)** K_d= 0.81-1.58 K_{oc}= 35 ± 0.5 K_f= 0.83 ± 1.0 K_{foc} = 35 ± 43.3 1/n = 0.89 ± 0.0 **North Carolina Loamy sand (1.2%OC, pH 5.7)** K_d=0.32-0.69 K_{oc}= 28 ± 1.0 K_f= 0.37 ± 1.0 K_{foc} = 31 ± 86.7 1/n = 0.86 ± 0.0 **Minnesota Clay loam (4.1%OC, pH 7.3)** K_d=0.41-1.07 K_{oc}= 11 ± 0.3 K_f= 0.45 ± 1.0 K_{foc} = 11 ± 25.4	Very highly mobile, indicates potential for leaching behaviour	2442056

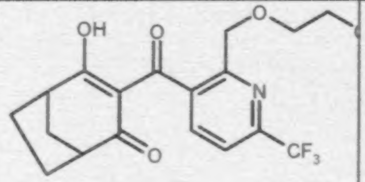
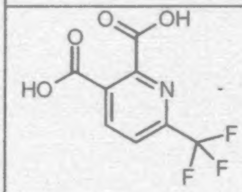
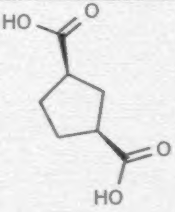
Study Type	**Study Endpoints/Information**	**COMMENTS**	**PMRA Number**
	1/n = 0.88 ± 0.0 **Iowa Sandy loam (4.4%OC, pH 6.6)** K_d=1.37-2.88 K_{oc}= 33 ± 0.6 K_f= 1.39 ± 1.1 K_{foc} = 32 ± 24.0 1/n = 0.89 ± 0.0 **Michigan Loamy sand (0.8%OC, pH 5.9)** K_d=0.17-0.41 K_{oc}= 24 ± 1.2 K_f= 0.22 ± 1.0 K_{foc} = 28 ± 2.3 1/n = 0.86 ± 0.0 **Ohio Loam (3.3%OC, pH 5.5)** K_d=0.33-1.58 K_{oc}= 10 ± 0.2 K_f= 0.35 ± 1.1 K_{foc} = 7 ± 31.8 1/n = 0.84 ± 0.0		
Adsorption in soil **(SYN503780** – metabolite)	Soils tested: Nebraska Silt loam, (1.6% OC, pH 6.9) Gartenacker Loam, (2.1% OC, pH 7.0) 18 Acres Sandy clay loam,(2.9% OC, pH 5.7) Marsillargues Silty clay, (1.0% OC, pH 7.7) No values determined due to lack of adsorption (all 4 soils).	indicates potential for leaching behaviour	2440906
Adsorption in soil **(CSAA806573** – metabolite)	Soils tested: Nebraska Silt loam, (1.6% OC, pH 6.9) Gartenacker Loam, (2.1% OC, pH 7.0) 18 Acres Sandy clay loam,(2.9% OC, pH 5.7) Marsillargues Silty clay, (1.0% OC, pH 7.7) No values determined due to lack of adsorption (all 4 soils).	indicates potential for leaching behaviour	2440905
Adsorption in soil **(CSCC163768** – metabolite)	**18 Acres Sandy clay loam,(2.9% OC, pH 5.7)** K_d=0.06 – 0.11 K_{oc}= 2.6 ± 0.1 K_f= 0.08 ± 1.1 K_{foc} = 2.8 ± 36.6 1/n = 0.96 ± 0.0	Very highly mobile, indicates potential for leaching behaviour	2440904

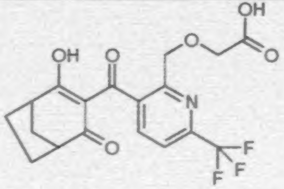
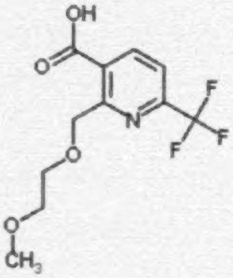
Study Type	Study Endpoints/Information	COMMENTS	PMRA Number
	Marsillargues Silty clay, (1.0% OC, pH 7.7) K_d=0.02-0.09 K_{oc}= 3.2 ± 0.4 K_f= 0.03 ± 1.1 K_{foc} = 3.4 ± 111.8 1/n = 0.81 ± 0.1 **Gartenacker Loam, (2.1% OC, pH 7.0)** **Nebraska Silt loam, (1.6% OC, pH 6.9)** No values determined due to lack of adsorption in these two additional soils.		
Adsorption in soil **(CSCD656832** – metabolite).	**Gartenacker Loam, (2.1% OC, pH 7.0)** K_d=4.75-7.90 K_{oc}= 233 ± 3.3 K_f=5.18 ± 1.0 K_{foc} = 247± 49.1 1/n = 0.92 ± 0.1 **18 Acres Sandy clay loam,(2.9% OC, pH 5.7)** K_d=31.69 - 85.76 K_{oc}= 1153 ± 43.2 K_f= 38.86 ± 1.1 K_{foc} = 1340 ± 36.6 1/n = 0.92 ± 0.1 **Marsillargues Silty clay, (1.0% OC, pH 7.7)** K_d=32.02-147.00 K_{oc}= 3575 ± 296.1 K_f= 51.79 ± 1.1 K_{foc} = 5179 ± 113.6 1/n = 0.79 ± 0.0 **Nebraska Silt loam, (1.6% OC, pH 6.9)** K_d= 82.22-260.50 K_{oc}= 5444 ± 277.7 K_f= 98.88 ± 1.1 K_{foc} = 6180 ± 68.3 1/n = 0.83 ± 0.0	Moderately to slightly mobile	2441388
Terrestrial Field Dissipation			
Terrestrial Field Dissipation (250EC – Iowa)	**Iowa, Ecozone 9.2, Clarion soil series, Sandy loam, pH 7.4** Half-life: 5.0 days (DFOP) DT_{90}: *ca* 55 days		2440922

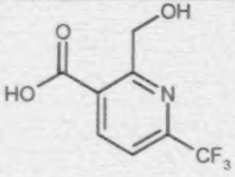
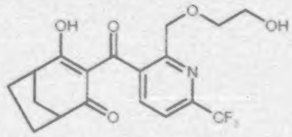
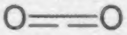
Study Type	Study Endpoints/Information	COMMENTS	PMRA Number
	Major transformation products detected: SYN503780 (20.4% at 3 and 7 DAT)		
Terrestrial Field Dissipation (250EC – Nebraska)	**Nebraska, Ecozone 9.2, Hastings soil series, Silt loam, pH 7.3** Half-life : 1.7 days (IORE) DT90: *ca* 36 days Major transformation products detected: SYN503780 (14.0% at 1 DAT)		2440918
	Prospective Groundwater		
Prospective Groundwater Study (TGAI – Lorsch, Germany, 2007-2012)	**Germany: sandy loam soil (0-15 cm) planted in corn for up to 1629 days** Bicyclopyrone residues were measured in all 8 down-gradient wells with residues of 0.04 µg/L first measured at 336 DAT. Maximum residues of 0.06 to 1.4 µg/L were measured at 1478-1629 DAT. Residues generally increased in all down-gradient wells throughout the study period. Method LOQ = 0.01µg/L SYN503780 first detected at 966 DAT, and subsequently was detected in 5 of the 8 down-gradient wells. Residues measured at 0.01 µg/L (1428 DAT) to a maximum of 0.11 µg/L at 1629 DAT	Expected to leach to groundwater	2440902
Prospective Groundwater Study (TGAI – Aba, Hungary)	**Hungary: loam/sandy loam soil depth to groundwater of 0.28-2.92 meters below ground surface, four applications, once per year over a 4 year period** Bicyclopyrone residues were measured in 4 of 8 down-gradient wells (LOQ = 0.01µg/L) first measured at 0.02 µg/L at 726 DAT. Maximum residues measured were 0.24 µg/L at 848 DAT SYN503780 not detected at >LOQ in any well. Data from the bromide	Expected to leach to groundwater	2440900

Study Type	Study Endpoints/Information	COMMENTS	PMRA Number
	tracer used indicate that the majority of added bicyclopyrone remains in the soil and would enter groundwater after the end of the study. The study therefore was too short to use except as a lower bound on bicyclopyrone concentrations in groundwater.		
Prospective Groundwater Study (TGAI – France, Alsace)	**France, silt loam soil (0-30 cm) planted in corn and with a depth to groundwater of 3.8 to 4.9 feet below ground surface for up to 1245 days** Bicyclopyrone residues were measured in 4 of 8 down-gradient wells. Bicyclopyrone first measured at 0.07 µg/L at 740 DAT and measured at a maximum of 0.11 µg/L at 951 DAT SYN503780 residues first detected at LOQ (0.01 µg/L) at 404-434 DAT, maximum residues of 0.03 µg/L measured at 1043, 1103 and 1131 days after treatment.	Expected to leach to groundwater	2440899
Prospective Groundwater Study (TGAI – Italy)	**Italy - loamy soil (USDS taxonomy order Alfisol, suborder Aqualfs) planted in corn for up to 1254 days** Bicyclopyrone first measured in all six down-gradient wells between 188 and 353 days posttreatment. Maximum residues detected were 0.34 µg/L at 589 DAT SYN503780 initially detected in 3 out of 6 down-gradient wells at the LOQ (0.01 µg/L) at 188-234 DAT. Maximum residues of 0.17 µg/L were measured in 2 wells at 807 and 868 DAT.	Expected to leach to groundwater	2440897

Table 8 Bicyclopyrone and Its Transformation Products

Structure	Transformation Product name (Nomenclature) and Chemical Identity	Study Type	Max % of Applied, days after treatment (DAT)	PMRA Number(s)
	**Bicyclopyrone** **IUPAC:** 4-hydroxy-3-[2-(2-methoxy-ethoxymethyl)-6-trifluoromethyl-pyridine-3-carbonyl]-bicyclo[3.2.1]oct-3-en-2-one **CAS:** 4-hydroxy-3-[[2-[(2-methoxyethoxy)methyl]-6-(trifluoromethyl)-3-pyridinyl]carbonyl]bicyclo[3.2.1]oct-3-en-2-one **CAS No.** 352010-68-5 **Formula:** $C_{19}H_{20}F_3NO_5$ **MW:** 399.36 g/mol **SMILES Code:** COCCOCc1c(ccc(n1)C(F)(F)F)C(=O)C2=C(C3CCC(C3)C2=O)O	Aerobic Soil Metabolism	n/a	2440937 2440939 2440941 2440931 2440927
		Anaerobic Soil Metabolism	n/a	2441352
		Aerobic Aquatic Metabolism	n/a	2441386 2441387
		Anaerobic Aquatic Metabolism	n/a	2441386 2441387
		Soil Photolysis	n/a	2440942
		Hydrolysis	n/a	2440945
		Aqueous Photolysis	n/a	2440944
		Terrestrial Field Dissipation	n/a	2440925 2440922 2440918
	**CSCC163768** **SYN504810** **IUPAC**: 6-(Trifluoromethyl)pyridine-2,3-dicarboxylic acid **CAS**: 6-trifluoromethyl-pyridine-2,3-dicarboxylic acid **CAS No**. 90376-94-6 **MW**: 235.1 g/mol **Formula**: $C_8 H_4F_3NO_4$ **SMILES:** c1cc(nc(c1C(=O)O)C(=O)O)C(F)(F)F	Aqueous photolysis	**26.6@ pH 5 (30)** **2.9@ pH 7 (30)** **3.0 in natural water (30)**	2440944
		Soil photolysis	**9.6 (30)**	2440942
		Aerobic Soil Metabolism	1.5 (92)	2440937 2440934
		Aerobic Aquatic Metabolism	2.8 (60)	2441386 2441387
		Anaerobic Aquatic Metabolism	9.1 (365)	2441386 2441387
		Terrestrial Field Dissipation	6.2 (3)	2440925 2440922 2440918
	**CSAA589691** **(NOA412101)** **IUPAC:** (1S,3R)-Cyclopentane-1,3-dicarboxylic acid **CAS**: (1S,3R)-Cyclopentane-1,3-dicarboxylic acid **CAS No**. 876-05-1 **Formula:** C7 H10 O4 **MW:** 158.1 g/mol **SMILES:** C1CC(CC1C(=O)O)C(=O)O	Aqueous Photolysis	26.3@pH 5 (18) **18.7@ pH 7 (30)** 14.5 natural water (30)	2440944
		Photolysis – soil	1.4 (0)	2440942

Structure	Transformation Product name (Nomenclature) and Chemical Identity	Study Type	Max % of Applied, days after treatment (DAT)	PMRA Number(s)
	**CSCD642512 (SYN545859)** **IUPAC:** 2-[[3-(2,4-Dioxobicyclo[3.2.1]octane-3-carbonyl)-6-(trifluoromethyl)-2-pyridyl]methoxy]acetic acid **CAS**: [3-(2-Hydroxy-4-oxo-bicyclo[3.2.1]oct-2-ene-3-carbonyl)-6-trifluoromethyl-pyridin-2-ylmethoxy]-acetic acid **Formula:** $C_{18}H_{16}F_3NO_6$ **MW**: 399.3 g/mol **SMILES:** c1cc(nc(c1C(=O)C2C(=O)C3CCC(C3)C2=O)COCC(=O)O)C(F)(F)F	Soil photolysis	**6.2 (30)**	2440942
		Aerobic Soil Metabolism	12.1 (92)	2440937 2440934
		Anaerobic Soil Metabolism	2.9 (89)	2441352
		Terrestrial Field Dissipation	2.5 (3)	2440925 2440922 2440918
	CSCD656832 (SYN545680) **IUPAC:** 3-Hydroxy-6-(trifluoromethyl)pyridine-2-carboxylic acid **CAS**: 3-Hydroxy-6-trifluoromethyl-pyridine-2-carboxylic acid **Formula:** $C_7H_4F_3NO_3$ **MW:** 207.1 g/mol **SMILES:** c1cc(nc(c1O)C(=O)O)C(F)(F)F	Soil photolysis	**4.8 (30)**	2440942
		Aerobic soil metabolism	14.4 (120)	2440937 2440934
		Terrestrial Field Dissipation	11.8% (21) (decreasing to 2.3% (180))	2440925
	**SYN503780 (CSAA794148)** **IUPAC:** 2-(2-Methoxy-ethoxymethyl)-6-(trifluoromethyl)-nicotinic acid **CAS**: 3-pyridinecarboxylic acid, 2-[(2-methoxyethoxy)methyl]-6-(trifluoromethyl) **Formula:** $C_{11}H_{12}F_3NO_4$ **MW:** 279.2 g/mol **SMILES:** COCCOCc1c(ccc(n1)C(F)(F)F)C(=O)O	Aqueous photolysis	6.3@ pH 5 (10) **2.9@ pH 7 (30)** **4.9 natural water (30)**	2440944
		Soil photolysis	62.5 (15)	2440942
		Aerobic Soil Metabolism	6.3 (50)	2440937 2440934
		Anaerobic Soil Metabolism	3.4 (60)	2441352
		Aerobic Aquatic Metabolism	2.9 (60)	2441386 2441387
		Anaerobic Aquatic Metabolism	4.3 (91)	2441386 2441387
		Terrestrial Field Dissipation	20.4 (3.7)	2440925 2440922 2440918

Structure	Transformation Product name (Nomenclature) and Chemical Identity	Study Type	Max % of Applied, days after treatment (DAT)	PMRA Number(s)
	**CSAA806573 (NOA451778)** **IUPAC:** 2-Hydroxymethyl-6-trifluoromethyl-nicotinic acid **CAS**: 2-Hydroxymethyl-6-trifluoromethyl-nicotinic acid **Formula:** C8 H6 F3 N O3 **MW:** 221.1 g/mol **SMILES:** c1cc(nc(c1C(=O)O)CO)C(F)(F)F	Aqueous photolysis	**5.5@ pH 5 (30)** **nd @ pH 7** **2.3 natural water (30)**	2440944
		Anaerobic Soil Metabolism	1.2 (119)	2441352
		Anaerobic Aquatic Metabolism	2.0 (91)	2441386 2441387
		Terrestrial Field Dissipation	3.5 (4)	2440925 2440922 2440918
	**CSAA915194 (NOA454598)** **IUPAC:** 4-Hydroxy-3-[2-(2-hydroxy-ethoxymethyl)-6-trifluoromethyl-pyridine-3-carbonyl]-bicyclo[3.2.1]oct-3-en-2-one **CAS**: 4-Hydroxy-3-[2-(2-hydroxy-ethoxymethyl)-6-trifluoromethyl-pyridine-3-carbonyl]-bicyclo[3.2.1]oct-3-en-2-one **Formula:** $C_{18}H_{18}F_3NO_5$ **MW:** 385.3g/mol **SMILES:** c1cc(nc(c1C(=O)C2=C(C3CCC(C3)C2=O)O)COCCO)C(F)(F)F	Aerobic Aquatic Metabolism	2.0 (105)	2441386 2441387
		Anaerobic Aquatic Metabolism	1.6 (182)	2441386 2441387
	Carbon dioxide **Formula:** CO_2 **MW:** 44.1 g/mol **SMILES:** O=C=O	Aqueous photolysis	4.7 @ pH 5 (30) 4.7 @ pH 7 (30) 0.6 natural water (30)	2440944
		Soil photolysis	20.1 (30)	2440942
		Aerobic Soil Metabolism	75.8 (365)	2440937 2440934
		Anaerobic Soil Metabolism	8.7 (89)	2441352
		Aerobic Aquatic Metabolism	4.5 (105)	2441386 2441387
		Anaerobic Aquatic Metabolism	7.0 (165)	2441386 2441387

Values shown in bold represent transformation products which reached their maximum levels at study termination

Table 9 Effects on Non-Target Species

Organism	Study type	Species	Test material	Endpoint	Value (effect)	Effect	Reference (PMRA #)
Terrestrial species							
Invertebrates	Acute oral	Honey bee (*Apis mellifera*)	NOA449280	48-h LD_{50}	>212.2 µg a.i./bee	mortality	2263381
			A16003E	48-h LD_{50}	>195.17 µg a.i./bee	mortality	2277412
	Acute contact	Honey bee (*Apis mellifera*)	NOA449280	48-h LC_{50}	>200 µg a.i./bee	mortality	2263381
			A16003E	48-h LC_{50}	>197.0 µg a.i./bee	mortality	2277412
		Earthworm (*Eisenia fetida*)	NOA449280	14-d LC_{50}	>1000mg a.i./kg soil	mortality	2263386
			A16003E	14-d LC_{50}	>1000 mg a.i./kg soil	mortality	2277414
		Parasitic wasp (*Aphidius rhopalosiphi*)	A15749AD	48-h LR_{50}	6.0 g a.i./ha	mortality	2263383
			A15936Z	48-h LR_{50}	>200 g a.i./ha	mortality	2263497
		Predatory mite (*Typhlodromus pyri*)	A15749AD	48-h LR_{50}	>200 g a.i./ha	mortality	2263422
	Reproduction	Predatory wasp (*Aphidius rhopalosiphi*)	A15749AD	NOER	10 g a.i./ha	reproduction	2263383
			A15936Z	NOER	200 g a.i./ha	reproduction	2263497
		Predatory mite (*Typhlodromus pyri*)	A15749AD	NOER	200 g a.i./ha	reproduction	2263422
Birds	Acute oral	Bobwhite quail (*Colinus virginianus*)	NOA449280	LD_{50}	1206 mg a.i./kg bw	mortality	2263338
			A16003E	LD_{50}	425.11 mg a.i./kg bw	mortality	2277418
		Canary (*Serinus canaria*)	NOA449280	LD_{50}	209 mg a.i./kg bw	mortality	2263335
	Dietary	Bobwhite quail (*Colinus virginianus*)	NOA449280	LC_{50}	>1495 mg a.i./kg diet	mortality	2263341
		Mallard duck (*Anas platyrhynchos*)	NOA449280	LC_{50}	>3020 mg a.i./kg diet	mortality	2263343
	Chronic	Bobwhite quail (*Colinus virginianus*)	NOA449280	LOEL	19.1 mg a.i./kg diet	reproduction	2263347
		Mallard duck (*Anas platyrhynchos*)	NOA449280	LOEL	4.3 mg a.i./kg diet	reproduction	2263350
Small wild mammals	Acute oral	Rat	NOA449280	LD_{50}	5000 mg/kg bw	mortality	2231610
	Multigenerational dietary reproduction	Rat	NOA449280	NOAEL	1.9 mg/kg bw/d	Offspring toxicity	2231684
Plants	Seedling emergence	11 plant species	A15749F	HR_5	5 g a.i. /ha	biomass	2263394
	Vegetative vigour				0.8 g a.i. /ha	biomass	2263397

Organism	Study type	Species	Test material	Endpoint	Value (effect)	Effect	Reference (PMRA #)
Freshwater Organisms							
Invertebrates	Acute	*Daphnia magna*	NOA449280	48-h EC_{50}	>93.3 mg a.i./L	immobility	2263358
			A16003E	48-h EC_{50}	>19.0 mg a.i./L		2277407
	Chronic	*Daphnia magna*	NOA449280	21-d NOEC	103.7 mg a.i./L		2263365
Fish	Acute	Rainbow trout (*Oncorhynchus mykiss*)	NOA449280	96-h LC_{50}	>93.7 mg a.i./L	mortality	2283600
			A16003E	96-h LC_{50}	>18.6 mg a.i./L	mortality	2277403
		Fathead minnow (*Pimephales promelas*)	NOA449280	96-h LC_{50}	>93.4 mg a.i./L	mortality	2263352
	Chronic (Early Life Stage)	Fathead minnow (*Pimephales promelas*)	NOA449280	33-d NOEC	10 mg a.i./L	growth	2263355
Algae	Acute	Green alga (*Pseudokirchneriella subcapitata*)	NOA449280	EC_{50}	2.4 mg a.i./L	growth and reproduction	2263369
			A16003E		2.0 mg a.i./L		2277408
Algae	Acute	Blue-green alga (*Anabaena flos-aquae*)	NOA449280	EC_{50}	>94.8 mg a.i./L	growth and reproduction	2263372
Diatom	Acute	Freshwater diatom (*Navicula pelliculosa*)	NOA449280	EC_{50}	9.8 mg a.i./L	growth and reproduction	2263376
Vascular plants	Acute	Duckweed (*Lemna gibba*)	NOA449280	7-d EC_{50}	0.013 mg a.i./L	growth	2263379
			A15749AD	7-d EC_{50}	0.0164 mg a.i./L	growth	2231938
			CSAA589691	7-d EC_{50}	>90.28 mg a.i./L	growth	2263495
			CSCC163768	7-d EC_{50}	>100.25 mg a.i./L	growth	2263468
Marine/Estuarine organisms							
Invertebrates	Acute	Mysid shrimp (*Americamysis bahia*)	NOA449280	96-h LC_{50}	3.4 mg a.i./L	mortality	2263360
		Eastern oyster (*Crassostrea virginica*)	NOA449280	96-h EC_{50}	37 mg a.i./L	shell deposition	2263362
Fish	Acute	Sheepshead minnow (*Cyprinodon variegates*)	NOA449280	96-h LC_{50}	>123 mg a.i./L	mortality	2263389
Diatom	Acute	Marine diatom (*Skeletonema costatum*)	NOA449280	EC_{50}	2.8 mg a.i./L	growth and reproduction	2263391

Table 10 Screening Level Risk Assessment on Aquatic and Terrestrial Non-Target Species Excluding Birds and Mammals

Organism	Exposure	Endpoint Value (mg a.i./L)	EEC (mg a.i./L)	RQ	Level of Concern
Freshwater species					
Invertebrates	Acute	$EC_{50}/2$: >46.65	0.0063	<0.1	Not exceeded
	Acute	$EC_{50}/2$: >9.5*	0.0063	<0.1	Not exceeded
	Chronic	NOEC: 103.7	0.0063	<0.1	Not exceeded
Fish	Acute	$LC_{50}/10$: >9.34	0.0063	<0.1	Not exceeded
	Early-life stage	NOEC: >1.86*	0.0063	<0.1	Not exceeded
	Short-term reproduction	NOEC: 10	0.0063	<0.1	Not exceeded
Amphibians	Acute, tadpoles	$LC_{50}/10$: >9.34	0.033	<0.1	Not exceeded
	Metamorphosis	NOEC: 10	0.033	<0.1	Not exceeded
Algae	Acute	$EC_{50}/2$: 1.2	0.0063	<0.1	Not exceeded
	Acute	$EC_{50}/2$: 1.0*	0.0063	<0.1	Not exceeded
Diatom	Acute	$EC_{50}/2$: 4.9	0.0063	<0.1	Not exceeded
Vascular plants (monocot, *Lemna gibba*)	Dissolved	$EC_{50}/2$: 0.0065	0.0063	0.97	Not exceeded
	Dissolved	$EC_{50}/2$: 0.0083**	0.0063	0.76	Not exceeded
	Dissolved	$EC_{50}/2$: >45.14[#]	0.0025	<0.1	Not exceeded
	Dissolved	$EC_{50}/2$: >50.13[##]	0.0037	<0.1	Not exceeded
Marine species					
Invertebrates	Acute	$EC_{50}/2$: 1.7	0.0063	<0.1	Not exceeded
Mollusk	Acute	$EC_{50}/2$: 18.5	0.0063	<0.1	Not exceeded
Fish	Acute	$LC_{50}/10$: >12.3	0.0063	<0.1	Not exceeded
Algae	Acute	$EC_{50}/2$: 1.4	0.0063	<0.1	Not exceeded
Terrestrial species					
Earthworm	Acute	$LC_{50}/2$: > 500 mg a.i./kg soil	0.02 mg a.i./kg soil	<0.1	Not exceeded
	Acute	$LC_{50}/2$: > 500 mg a.i./kg soil*	0.02 mg a.i./kg soil	<0.1	Not exceeded
Bee	Oral[1]	LD_{50}: > 212.2 µg a.i./bee	0.050 kg a.i./ha × 29 µg a.i./bee per kg/ha = 1.45 µg a.i./bee	<0.1	Not exceeded
		LD_{50}: > 195.2 µg a.i./bee*	0.050 kg a.i./ha × 29 µg a.i./bee per kg/ha = 1.45 µg a.i./bee	<0.1	Not exceeded
	Contact[2]	LD_{50}: > 200 µg a.i./bee	0.050 kg a.i./ha × 2.4 µg a.i./bee per kg/ha = 0.12 µg a.i./bee	<0.1	Not exceeded
		LD_{50}: > 197.0 µg	0.050 kg	<0.1	Not exceeded

Organism	Exposure	Endpoint Value (mg a.i./L)	EEC (mg a.i./L)	RQ	Level of Concern
		a.i./bee*	a.i./ha × 2.4 µg a.i./bee per kg/ha = 0.12 µg a.i./bee		
Predatory arthropod, *Typhlodromus pyri*	Contact, glass plate	LR_{50}: >200 g a.i./ha**	In-field: 50 g a.i./ha	0.3	Not exceeded
			Off-field: (ground appl., 6% drift) 3 g a.i./ha	<0.1	Not exceeded
Parasitoid arthropod, *Aphidius rhopalosiphi*	Contact, glass plate	LR_{50}: 6.0 g a.i./ha**	In-field: 50 g a.i./ha	8.3	Exceeded
			Off-field: (ground appl., 6% drift) 3 g a.i./ha	0.5	Not exceeded
Parasitoid arthropod, *Aphidius rhopalosiphi*	Barley plant	LR_{50}: >200 g a.i./ha***	In-field: 50 g a.i./ha	0.3	Not exceeded
			Off-field: (ground appl., 6% drift) 3 g a.i./ha	<0.1	Not exceeded
Vascular plant	Vegetative vigour	HD_5 of SSD for ER_{50} values: 0.8 g a.i./ha	In-field: 50 g a.i./ha	62.5	Exceeded
			Off-field: (ground appl., 6% drift) 3 g a.i./ha	3.8	Exceeded

*test material A16003E

** test material A15749AD

*** test material A15936Z

[#] transformation product, CSAA589691 (assuming 100% transformation from bicyclopyrone)

[##] transformation product, CSCC163769 (assuming 100% transformation from bicyclopyrone)

[1] Oral exposure as per Rortais et al (2005) and Crailsheim et al (1992 and 1993), the maximum single field application rate is converted to an amount of active ingredient that forager bees will consume via nectar consumption rates i.e. maximum single field application rate (kg a.i./ha) multiplied by 29 µg a.i./bee per kg/ha.

[2] Contact exposure endpoint converted to field rate as per Koch and Weiber 1997, i.e. maximum single application rate in kg × 2.4 µg a.i./bee

Table 11 Screening Level Risk Assessment on Non-Target Species for Birds and Small Wild Mammals

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE (mg a.i./kg bw)[1]	RQ	Level of Concern
Small Bird (0.02 kg)					
Acute	20.9	Insectivore (small insects)	4.07	0.2	Not exceeded
Reproduction	4.3	Insectivore (small insects)	4.07	0.9	Not exceeded
Medium Sized Bird (0.1 kg)					
Acute	20.9	Insectivore (small insects)	3.18	0.2	Not exceeded
Reproduction	4.3	Insectivore (small insects)	3.18	0.7	Not exceeded
Large Sized Bird (1 kg)					
Acute	20.9	Herbivore (short grass)	2.05	0.1	Not exceeded
Reproduction	4.3	Herbivore (short grass)	2.05	0.5	Not exceeded
Small Mammal (0.015 kg)					
Acute	500.00	Insectivore	2.34	0.005	Not exceeded
Reproduction	1.90	Insectivore	2.34	1.23	Exceeded
Medium Sized Mammal (0.035 kg)					
Acute	500.00	Herbivore (short grass)	4.54	0.01	Not exceeded
Reproduction	1.90	Herbivore (short grass)	4.54	2.39	Exceeded
Large Sized Mammal (1 kg)					
Acute	500.00	Herbivore (short grass)	2.43	0.005	Not exceeded
Reproduction	1.90	Herbivore (short grass)	2.43	1.28	Exceeded

[1] EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/BW) × EEC, where:

FIR: Food Ingestion Rate (Nagy, 1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:

Passerine Equation (body weight < or = 200 g): FIR (g dry weight/day) = $0.398(\text{BW in g})^{0.850}$

All birds Equation (body weight > 200 g): FIR (g dry weight/day) = $0.648(\text{BW in g})^{0.651}$.

For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = $0.235(\text{BW in g})^{0.822}$

BW: Generic Body Weight

EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher *et al.* (1994). At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

Table 12 Expanded Screening Level Risk Assessment for Birds

			Maximum nomogram residues			
			On-field		**Off Field**	
	Toxicity (mg a.i./kg bw/d)	**Food Guild (food item)**	**EDE (mg a.i./kg bw)**	**RQ**	**EDE (mg a.i./kg bw)**	**RQ**
Small Bird (0.02 kg)						
Acute	20.90	Insectivore	4.07	0.19	0.24	0.01
	20.90	Granivore (grain and seeds)	0.63	0.03	0.04	0.00
	20.90	Frugivore (fruit)	1.26	0.06	0.08	0.00
Dietary	149.50	Insectivore	4.07	0.03	0.24	0.00
	149.50	Granivore (grain and seeds)	0.63	0.00	0.04	0.00
	149.50	Frugivore (fruit)	1.26	0.01	0.08	0.00
Reproduction	4.30	Insectivore	4.07	0.95	0.24	0.06
	4.30	Granivore (grain and seeds)	0.63	0.15	0.04	0.01
	4.30	Frugivore (fruit)	1.26	0.29	0.08	0.02
Medium Sized Bird (0.1 kg)						
Acute	20.90	Insectivore	3.18	0.15	0.19	0.01
	20.90	Granivore (grain and seeds)	0.49	0.02	0.03	0.00
	20.90	Frugivore (fruit)	0.98	0.05	0.06	0.00
Dietary	149.50	Insectivore	3.18	0.02	0.19	0.00
	149.50	Granivore (grain and seeds)	0.49	0.00	0.03	0.00
	149.50	Frugivore (fruit)	0.98	0.01	0.06	0.00
Reproduction	4.30	Insectivore	3.18	0.74	0.19	0.04
	4.30	Granivore (grain and seeds)	0.49	0.11	0.03	0.01
	4.30	Frugivore (fruit)	0.98	0.23	0.06	0.01
Large Sized Bird (1 kg)						
Acute	20.90	Insectivore	0.93	0.04	0.06	0.00
	20.90	Granivore (grain and seeds)	0.14	0.01	0.01	0.00
	20.90	Frugivore (fruit)	0.29	0.01	0.02	0.00
	20.90	Herbivore (short grass)	2.05	0.10	0.12	0.01
	20.90	Herbivore (long grass)	1.25	0.06	0.08	0.00
	20.90	Herbivore (Broadleaf plants)	1.90	0.09	0.11	0.01
Dietary	149.50	Insectivore	0.93	0.01	0.06	0.00
	149.50	Granivore (grain and seeds)	0.14	0.00	0.01	0.00
	149.50	Frugivore (fruit)	0.29	0.00	0.02	0.00
	149.50	Herbivore (short grass)	2.05	0.01	0.12	0.00
	149.50	Herbivore (long grass)	1.25	0.01	0.08	0.00
	149.50	Herbivore (Broadleaf plants)	1.90	0.01	0.11	0.00
Reproduction	4.30	Insectivore	0.93	0.22	0.06	0.01
	4.30	Granivore (grain and seeds)	0.14	0.03	0.01	0.00
	4.30	Frugivore (fruit)	0.29	0.07	0.02	0.00
	4.30	Herbivore (short grass)	2.05	0.48	0.12	0.03
	4.30	Herbivore (long grass)	1.25	0.29	0.08	0.02
	4.30	Herbivore (Broadleaf plants)	1.90	0.44	0.11	0.03

Table 13 Expanded Screening Level Risk Assessment on Reproduction of Small Wild Mammals

			Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field		On-field		Off Field	
	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	EDE (mg a.i./kg bw)^1	RQ	EDE (mg a.i./kg bw)^1	RQ	EDE (mg a.i./kg bw)^1	RQ	EDE (mg a.i./kg bw)^1	RQ
Small Mammal (0.015 kg)										
Reproduction	1.9	Insectivore	2.3	1.2*	0.1	0.1	1.6	0.9	0.1	0.1
	1.9	Granivore (grain and seeds)	0.4	0.2	0.02	0.01	0.2	0.1	0.01	0.01
	1.9	Frugivore (fruit)	0.7	0.4	0.04	0.02	0.34	0.2	0.02	0.01
Medium Sized Mammal (0.035 kg)										
Reproduction	1.9	Insectivore	2.1	1.1*	0.1	0.1	1.4	0.8	0.1	0.04
	1.9	Granivore (grain and seeds)	0.3	0.2	0.02	0.01	0.2	0.1	0.01	0.005
	1.9	Frugivore (fruit)	0.6	0.3	0.04	0.02	0.3	0.2	0.02	0.01
	1.9	Herbivore (short grass)	4.5	2.4*	0.3	0.1	1.6	0.8	0.1	0.05
	1.9	Herbivore (long grass)	2.8	1.5*	0.2	0.1	0.9	0.5	0.05	0.03
	1.9	Herbivore (Broadleaf plants)	4.2	2.2*	0.3	0.1	1.4	0.7	0.1	0.04
Large Sized Mammal (1 kg)										
Reproduction	1.9	Insectivore	1.1	0.6	0.1	0.04	0.8	0.4	0.05	0.02
	1.9	Granivore (grain and seeds)	0.2	0.1	0.01	0.005	0.1	0.04	0.005	0.003
	1.9	Frugivore (fruit)	0.3	0.2	0.02	0.01	0.2	0.1	0.01	0.005
	1.9	Herbivore (short grass)	2.4	1.3*	0.2	0.1	0.9	0.5	0.05	0.03
	1.9	Herbivore (long grass)	1.5	0.8	0.1	0.05	0.5	0.3	0.03	0.02
	1.9	Herbivore (Broadleaf plants)	2.2	1.2*	0.1	0.1	0.7	0.4	0.05	0.02

1 EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/BW) × EEC, where:

FIR: Food Ingestion Rate (Nagy, 1987). For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235(BW in g) 0.822

BW: Generic Body Weight

EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher *et al.* (1994). At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

*exceeds the level of concern of 1.0. All other calculated risk quotient values do not exceed the level of concern.

Figure 1 **Transformation Pathway for Bicyclopyrone in Soil Under Aerobic Conditions**

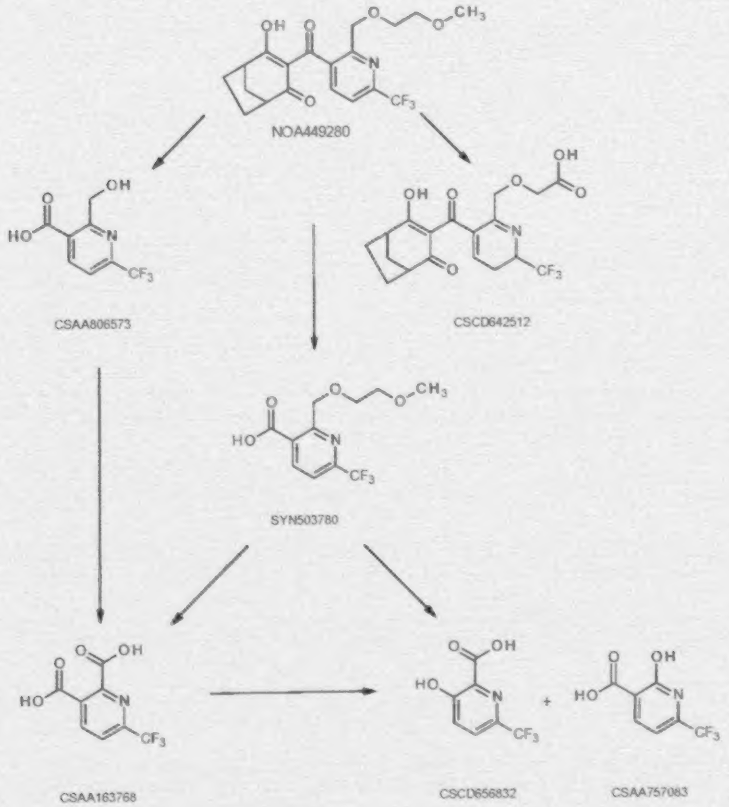


Figure 2 **Photolysis Transformation Pathway of Bicyclopyrone in Water**

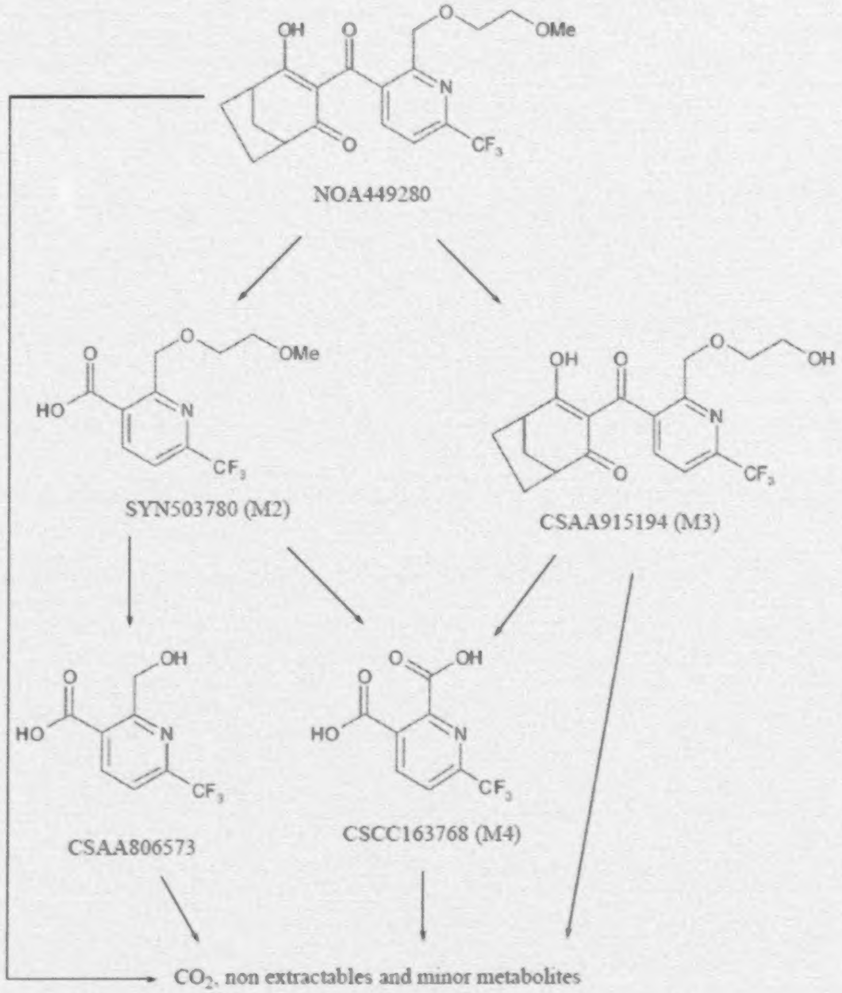


Table 14 Use (label) Claims Proposed by Applicant and Whether Acceptable or Unsupported

a) Use Claims That Are Supported for SYNA16003 Herbicide

Items	Use claims that are supported
Use sites/crops	Corn (field, seed and sweet), as proposed.
Appl. rate	37.5 to 50 g a.i./ha, as proposed (rate dependant on weed species).
No. of apps	One per season, as proposed.
Use range	Eastern Canada, as proposed.
Weed claims	Short-season residual control of velvetleaf, eastern black nightshade, common ragweed, redroot pigweed and lambs'-quarters and early-season suppression of proso millet, as proposed.

Items	Use claims that are supported
Appl. timing	Relative to crop: pre-emergence and post-emergence (up to 6 leaf corn), as proposed. Relative to weeds: pre-emergence, as proposed.
Appl. method	Apply in a minimum of 100 L of carrier (water or UAN) per hectare by ground equipment, as proposed.
Tank mix partners	Pre-emergence (to crop) application timing: • Primextra II Magnum Herbicide; 2500, 3000 and 4000 g a.i./ha - field corn only (as proposed); • Lumax EZ Herbicide; 3350 g a.i./ha - field corn only (as proposed); 4700 g a.i./ha – field, seed and sweet corn (as proposed). Post-emergence (to crop) application timing: • Primextra II Magnum Herbicide (from spike to 6 leaf); 3000 – 4000 g a.i./ha - field corn only (as proposed); • Lumax EZ Herbicide (up to and including 2 leaf corn); 4700 g a.i./ha - field corn only (as proposed); • Touchdown Total Herbicide or equivalent 900 g a.e. glyphosate/ha (up to and including 6 leaf corn); glyphosate tolerant field corn only (as proposed); • Touchdown Total Herbicide or equivalent 900 g a.e. glyphosate/ha + Primextra II Magnum Herbicide (up to and including 6 leaf corn); glyphosate tolerant field corn only (as proposed).
Rotational crops (months after application)	Winter wheat (4 months), field corn (10 months), seed corn (10 months), sweet corn (10 months), spring wheat (10 months), spring barley (10 months) and soybeans (non-sand based soils; 11 months), as proposed (except for soybean). May also re-plant to field, seed or sweet corn in the event of a crop failure (as proposed).

b) Use Claims That Are Supported for Acuron Herbicide

Items	Use claims that are supported
Use sites/crops	Corn (field, seed and sweet), as proposed.
Appl. rate	2025 g a.i./ha, as proposed.
No. of apps	One, as proposed.
Use range	Eastern Canada, as proposed.
Weed claims	Season-long control of nightshade (American, eastern black), common ragweed, lady's-thumb, lamb's-quarters, redroot pigweed, velvetleaf, wild buckwheat, wild mustard, barnyard grass, crabgrass (smooth, hairy), fall panicum, foxtail (green, yellow, giant) and witchgrass and early-season suppression of proso millet, as proposed.

Appl. timing	Relative to crop: pre-emergence and post-emergence (up to 2 leaf corn), as proposed. Relative to weeds: prior to proso millet emergence and before other grass weeds exceed the 2 leaf stage.
Appl. method	Apply in a minimum of 150 L of carrier (water or UAN) per hectare by ground equipment, as proposed.
Tank mix partners	None proposed.
Rotational crops (months after application)	Winter wheat (4.5 months), field corn (no restriction), seed corn (no restriction), sweet corn (no restriction), spring wheat (10 months) and soybeans (non-sand based soils; 11 months), as proposed (except for soybean). May also re-plant to field, seed or sweet corn in the event of a crop failure (as proposed)

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

Table 1 Differences Between MRLs in Canada and in Other Jurisdictions

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

Bicyclopyrone is a new active ingredient which is concurrently being registered in Canada and the United States. The MRLs proposed for bicyclopyrone in Canada are the same as corresponding tolerances to be promulgated in the United States, except for certain livestock commodities [fat, meat and meat by-products of cattle, goats, hogs, horses, sheep and poultry, milk and egg all at 0.02 ppm], for which differences in MRLs/tolerances may be due to different livestock feed items/practices, or different policies on setting MRLs/tolerances on commodities with no expectation of quantifiable residues.

Once established, the American tolerances for bicyclopyrone will be listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide.

Currently, there are no Codex MRLs[10] listed for bicyclopyrone in or on any commodity on the Codex Alimentarius Pesticide Residues in Food website.

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items/practices, or different policies on setting MRLs/tolerances on commodities with no expectation of quantifiable residues.

---

[10] The Codex Alimentarius Commission is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
2231461	2007, NOA449280 - Melting point / boiling point, DACO: 2.14.13,2.14.4,2.14.5,IIA 2.1.1,IIA 2.1.2,IIA 2.1.3 CBI
2231464	2010, Bicyclopyrone - Safety study, DACO: 2.16,IIA 2.11.1,IIA 2.11.2,IIA 2.13,IIA 2.15 CBI
2231466	2010, Bicyclopyrone - Safety study, DACO: 2.16,IIA 2.11.1,IIA 2.11.2,IIA 2.13,IIA 2.15 CBI
2231468	2009, Bicyclopyrone - Surface tension, DACO: 2.16,IIA 2.14 CBI
2231472	2009, Bicyclopyrone - Surface tension, DACO: 2.16,IIA 2.14 CBI
2231474	2009, Bicyclopyrone - pH of aqueous solutions, DACO: 2.16,IIA 2.16 CBI
2231476	2009, Bicyclopyrone - pH of aqueous solutions, DACO: 2.16,IIA 2.16 CBI
2231478	2012, Bicyclopyrone - Chemical stability of batch SMU9JP020 after storage in PE bag for 3 months/20 C, 6 months/20 C, 9 months/20 C and 1 year/20 C, DACO: 2.14.14,IIA 2.17.1 CBI
2231480	2012, Bicyclopyrone - Chemical stability of batch SMU9GP012 after storage in PE bag for 3 months/20 C, 9 months/20 C and 1 year/20 C, DACO: 2.14.14,IIA 2.17.1 CBI
2231484	2010, Bicyclopyrone - Thermal stability / stability in air, DACO: 2.14.13,IIA 2.17.2 CBI
2231486	2010, Bicyclopyrone - Thermal stability / stability in air, DACO: 2.14.13,IIA 2.17.2 CBI
2231493	2010, Bicyclopyrone - Chemical characteristics (metal stability) after storage for 7 days/20 C, 7 days/40 C, 14 days/20 C and 14 days/40 C in glass, DACO: 2.14.13,IIA 2.17.2 CBI
2231495	2012, Bicyclopyrone - Chemical characteristics (metal stability) after storage for 7 days/20 C, 7 days/40 C, 14 days/20 C and 14 days/40 C in glass, DACO: 2.14.13,IIA 2.17.2 CBI
2231496	2012, Bicyclopyrone - Chemical characteristics (metal-ion stability) after storage for 7 days and 14 days at 20 C and 40 C in glass, DACO: 2.14.13,IIA 2.17.2 CBI

2231497	2012, Bicyclopyrone - Chemical characteristics (metal-ion stability) after storage for 7 days and 14 days at 20 C and 40 C in glass, DACO: 2.14.13,IIA 2.17.2 CBI
2231500	2009, Bicyclopyrone - Complex formation ability according to OECD 108, DACO: 2.16,IIA 2.18 CBI
2231501	2009, Bicyclopyrone - Complex formation ability according to OECD 108, DACO: 2.16,IIA 2.18 CBI
2231504	2010, Bicyclopyrone - Particle size distribution, DACO: 2.16,IIA 2.18 CBI
2231506	2010, Bicyclopyrone - Particle size distribution, DACO: 2.16,IIA 2.18 CBI
2231508	2012, Bicyclopyrone - Oxidation/reduction: Chemical incompatibility, DACO: 2.16,IIA 2.18 CBI
2231509	2012, NOA449280 tech. - Corrosion characteristics of batch SMU9GP012 after storage in PE bag for 1 month, 6 months and 1 year at 20 C, DACO: 2.16,IIA 2.18 CBI
2231512	2012, NOA449280 tech. - Corrosion characteristics of batch SMU9JP020 after storage in PE bag for 1 month, 6 months and 1 year at 20 C, DACO: 2.16,IIA 2.18 CBI
2231515	2012, Bicyclopyrone - Determination of density, DACO: 2.14.6,IIA 2.2 CBI
2231517	2007, NOA449280 - Determination of the relative density, DACO: 2.14.6,IIA 2.2 CBI
2231520	2012, Bicyclopyrone - Determination of Density, DACO: 2.14.6,IIA 2.2 CBI
2231522	2007, NOA449280: Vapour pressure, DACO: 2.14.9,IIA 2.3.1 CBI
2231523	2010, Bicyclopyrone - Henry's law constant, DACO: 2.16,IIA 2.3.2 CBI
2231525	2007, NOA449280 - Color, physical state and odor, DACO: 2.14.1,2.14.2,2.14.3,IIA 2.4.1,IIA 2.4.2 CBI
2231527	2009, Bicyclopyrone - Color, physical state and odor, DACO: 2.14.1,2.14.2,2.14.3,IIA 2.4.1,IIA 2.4.2 CBI
2231529	2009, Bicyclopyrone - Color, physical state and odor, DACO: 2.14.1,2.14.2,2.14.3,IIA 2.4.1,IIA 2.4.2 CBI
2231531	2010, NOA449280 - Spectra, DACO: 2.12.1,2.12.2,2.13.2,2.14.12,IIA 2.5.1,IIA 2.5.1.1,IIA 2.5.1.2,IIA 2.5.1.3,IIA 2.5.1.4,IIA 2.5.1.5,IIA 2.5.1.6,IIA 2.5.2 CBI
2231534	2009, NOA449280 - Determination of the water solubility, DACO: 2.14.7,IIA 2.6 CBI

2231537	2010, Bicyclopyrone - Solubility in organic solvents, DACO: 2.14.8,IIA 2.7 CBI
2231539	2010, Bicyclopyrone - Solubility in organic solvents, DACO: 2.14.8,IIA 2.7 CBI
2231542	2008, NOA449280 - Determination of the partition coefficient (n-octanol/water), DACO: 2.14.11,IIA 2.8.1,IIA 2.8.2 CBI
2231548	2007, NOA449280 - Dissociation constant in water, DACO: 2.14.10,8.2.3.2,IIA 2.9.5 CBI
2231588	2011, NOA449280 - Validation of an Analytical Method (Draft GRM030.06A) for the Determination of NOA449280 and its Metabolites SYN503780, CSCC163768, CSCD656832, CSCD642512 and CSAA806573 in Water, DACO: 8.2.2.3,IIA 4.5
2231590	2012, NOA449280 - Residue Method GRM030.06A for the Determination of NOA449280 and its Metabolites SYN503780, CSCC163768 , CSCD656832, CSCD642512 and CSAA806573 in Water, DACO: 8.2.2.3,IIA 4.5
2231448	2012, Bicylcopyrone MII Section 2 (GJR) Analytical methods, DACO: 12.7,Document M
2231551	2010, Bicyclopyrone tech. - Assay by HPLC, DACO: 2.13.1,IIA 4.2.1
2231549	2012, Bicyclopyrone - Validation of analytical method SA-48/1, DACO: 2.13.1,IIA 4.2.1
2231440	2012, NOA449280 - Document J - Confidential Information, DACO: 2.11.1,2.11.2,2.11.3,2.11.4,2.12.1,2.12.2,2.13.3,2.13.4,2.16,Document J,IIA 1.10.1,IIA 1.10.2,IIA 1.11.1,IIA 1.11.2,IIA 1.12,IIA 1.8.1,IIA 1.8.2,IIA 1.9.1.1,IIA 1.9.1.2,IIA 1.9.2,IIA 1.9.3,II
2231439	2012, Bicyclopyrone (NOA449280) - Confidential Studies - Sept 2012, DACO: 2.13.1,2.13.3,2.13.4,2.16,Document J CBI
2231575	2007, NOA449280 - Residue Method for the Determination of NOA449280 and Metabolite SYN503780 in soil, DACO: 8.2.2.1,IIA 4.4
2231579	2007, Validation of a Method (Draft GRM030.02A) for the Determination of NOA449280 and SYN503780 in Soil, DACO: 8.2.2.1,IIA 4.4
2231584	2010, Independent Laboratory Validation - Analytical Method GRM030.02A for the Determination of NOA449280 and Metabolite SYN503780 in Soil, DACO: 8.2.2.1,IIA 4.4
2231578	2009, NOA449280 - Residue Analytical method for the Determination of NOA449280 and its Metabolites SYN503780, CSCD656832, CSCD642512, CSCC163768 and CSAA806573 in Soil. Final Determination by LC-MS/MS, DACO: 8.2.2.1,IIA 4.4

2231583	2009, NOA449280 - Validation of Analytical Method GRM030.04A for the Determination of Residues of NOA449280 and Metabolites SYN503780, CSCD656832, CSCD642512, CSCC163768 and CSAA806573 in Soil, DACO: 8.2.2.1,IIA 4.4
2231582	2009, NOA449280 - Validation of Draft Method GRM030.04A for the Determination of NOA449280, SYN503780, CSCC163768, CSCD656832, CSCD642512 and CSAA806573 in Soil, DACO: 8.2.2.1,IIA 4.4
2231585	2008, NOA449280 - Residue Method for the Determination of NOA449280 and SYN503780 in Water. Final Determination by LC-MS/MS, DACO: 8.2.2.3,IIA 4.5
2231587	2008, NOA449280 - Validation of a Method (Draft GRM030.01A) for the Determination of NOA449280 and SYN503780 in Drinking, Surface and Ground Water, DACO: 8.2.2.3,IIA 4.5
2231591	2012, NOA449280 - Independent Laboratory Validation of Analytical Method GRM030.01A for the Determination of NOA449280 and SYN503780 Residues in Water, DACO: 8.2.2.3,IIA 4.5
2231590	2012, NOA449280 - Residue Method GRM030.06A for the Determination of NOA449280 and its Metabolites SYN503780, CSCC163768 , CSCD656832, CSCD642512 and CSAA806573 in Water, DACO: 8.2.2.3,IIA 4.5
2231588	2011, NOA449280 - Validation of an Analytical Method (Draft GRM030.06A) for the Determination of NOA449280 and its Metabolites SYN503780, CSCC163768, CSCD656832, CSCD642512 and CSAA806573 in Water, DACO: 8.2.2.3,IIA 4.5
2231594	2012, NOA449280 - Analytical Method GRM030.07A for the Determination of NOA449280 in Air, DACO: 8.2.2,IIA 4.7
2231572	2012, NOA449280 EC (A13765C) - Field Accumulation in Rotational Crops (90-, 150- and 270-Day PBI) USA, 2008, DACO: 7.2.1,7.2.4,7.4.4,IIA 4.3,IIA 6.6.3
2233144	2012, A19707A - Document MIII Section 1- Identity and PhysChem Properties, DACO: 12.7,Document M
2234430	2012, A16003E Document MIII Section 1 - Identity, physical and chemical properties, further information and proposed classification, DACO: 12.7,Document M
2234507	2010, A16003E - Corrosion characteristics of batch J8308/145 after storage in packaging made of HDPE for 1 year at 20C, DACO: 3.5.5,IIIA 2.14 CBI

2234509	2010, A16003E - Corrosion characteristics of batch J8308/145 after storage in packaging made of PET for 1 year at 20C, DACO: 3.5.5,IIIA 2.14 CBI
2234532	2011, A16003E - Chemical stability of batch J8308/145 after storage in packaging made of HDPE for 1 year at 20C, DACO: 3.5.10,IIIA 2.7.2 CBI
2234539	2009, A16003E - Technical properties of batch J8308/145, DACO: 3.5.10,8.2.3.6,IIIA 2.7.4,IIIA 2.8.2,IIIA 2.8.4 CBI
2276152	2012, A19707A - Color, Odor, Physical State, pH, Density and Viscosity, DACO: 3.5.1,3.5.2,3.5.3,3.5.6,3.5.7,3.5.9,IIIA 2.1,IIIA 2.4.2,IIIA 2.5.2,IIIA 2.6.1 CBI
2276154	2012, A19707A - Safety Study, DACO: 3.5.11,3.5.12,3.5.8,IIIA 2.2.1,IIIA 2.2.2,IIIA 2.3.1,IIIA 2.3.2,IIIA 2.3.3 CBI
2276155	2012, A19707A - Oxidation/Reduction: Chemical incompatibility, DACO: 3.7,IIIA 2.15 CBI
2277360	2009, A16003E - Physical properties of batch J8308/145, DACO: 3.5.1,3.5.13,3.5.14,3.5.2,3.5.3,3.5.6,3.5.7,3.5.9,3.7,IIIA 2.1,IIIA 2.11,IIIA 2.13,IIIA 2.4.1,IIIA 2.4.2,IIIA 2.5.2,IIIA 2.5.3,IIIA 2.6.1 CBI
2277362	2009, A16003E - Safety study, DACO: 3.5.11,3.5.12,3.5.8,IIIA 2.2.1,IIIA 2.2.2,IIIA 2.3.1,IIIA 2.3.2,IIIA 2.3.3 CBI
2277364	2009, A16003E - Storage stability and shelf life statement (2 weeks 54C) in packaging made of PET, DACO: 3.5.10,IIIA 2.7.1,IIIA 2.7.5 CBI
2277366	2009, A16003E - Storage stability and shelf life statement (2 weeks 54C) in packaging made of HDPE, DACO: 3.5.10,IIIA 2.7.1,IIIA 2.7.4 CBI
2277368	2012, A16003E - Storage Stability and Shelf Life Statement (2 years 25C) in packaging made of HDPE, DACO: 3.5.10,IIIA 2.7.2,IIIA 2.7.5 CBI
2277371	2012, A16003E - Storage Stability and Shelf Life Statement (2 years 25C) in packaging made of PET, DACO: 3.5.10,IIIA 2.7.2,IIIA 2.7.5 CBI
2277401	2011, A16003E - Chemical stability of batch J8308/145 after storage in packaging made of HDPE for 1 year at 20, DACO: 3.5.10,IIIA 2.7.2 CBI
2277411	2009, A16003E - Oxidation/reduction: Chemical incompatibility, DACO: 3.7,IIIA 2.15 CBI
2384204	2014, ACURON herbicide- Response to PMRA chemistry clarification, DACO: 3.5.10,3.5.14,3.5.5,3.5.9 CBI
2428336	2014, Mesotrione/atrazine/S-metolachlor/bicyclopyrone ZC (A19707A)- One year storage stability at ambient temperature and corrosion characteristics- Addendum to MRID 48758219, DACO: 3.5.10,3.5.14 CBI

2233146	2012, A19707A - Document MIII Section 2 - Analytical Methods, DACO: 12.7,Document M
2233213	2012, Analytical Method SF-552/2 - Determination of CGA77102, G30027, NOA449280, ZA1296 and CGA154281 in A19707A, DACO: 3.4.1,IIIA 5.2.1
2234431	2012, A16003E - Document MIII Section 2 - Analytical Methods, DACO: 12.7,Document M
2277391	2009, A16003E - Validation of Analytical Method SF-338/1, DACO: 3.4.1,IIIA 5.2.1
2233134	2012, A19707A - Document J - Confidential Information, DACO: 0.8.11,0.8.12,3.2.1,3.2.2,3.2.3,3.3.1,3.3.2,Document J,IIIA 1.4.1,IIIA 1.4.2,IIIA 1.4.3.1,IIIA 1.4.3.2,IIIA 1.4.3.3,IIIA 1.4.4,IIIA 1.4.5.1,IIIA 1.4.5.2
2233144	2012, A19707A - Document MIII Section 1- Identity and PhysChem Properties, DACO: 12.7,Document M
2234419	2012, A16003E Document J Confidential Information, DACO: 0.8.11,0.8.12,3.2.1,3.2.2,3.2.3,3.3.1,3.3.2,Document J,IIIA 1.4.1,IIIA 1.4.2,IIIA 1.4.3.1,IIIA 1.4.3.2,IIIA 1.4.3.3,IIIA 1.4.4,IIIA 1.4.5.1,IIIA 1.4.5.2
2234430	2012, A16003E Document MIII Section 1 - Identity, physical and chemical properties, further information and proposed classification, DACO: 12.7,Document M

2.0 Human and Animal Health

PMRA Document Number	Reference
2231598	2010, [14C]-NOA449280 - Tissue Depletion in the Rat Following a Single Oral Administration, DACO: 4.5.9,IIA 5.1.1
2231600	2009, [14C]NOA449280 An Investigation into the Pharmacokinetics Following Single Oral and Intravenous Administration to the Rat., DACO: 4.5.9,IIA 5.1.1
2231602	2010, [14C]-NOA449280 - An Investigation into Absorption, Distribution, Metabolism and Biliary Excretion Following a Single Oral Administration to the Rat, DACO: 4.5.9,IIA 5.1.1
2231604	2009, [14C]-NOA449280 - Excretion and Tissue Distribution Following Single Oral or Intravenous Administration to the Rat, DACO: 4.5.9,IIA 5.1.1,IIA 5.1.2
2231606	2010, [14C]-NOA449280 - Excretion and Tissue Distribution Following Repeated Oral Administration to the Rat, DACO: 4.5.9,IIA 5.1.3

2231608	2012, NOA449280 - A 28-Day Dietary Immunotoxicity Study in CD-1 Female Mice, DACO: 4.2.9,4.3.8,4.4.5,4.5.8,4.8,IIA 5.10
2231610	2007, NOA449280 - Acute Oral Toxicity Study In The Rat (Up and Down Procedure), DACO: 4.2.1,IIA 5.2.1
2231613	2007, NOA449280- Acute Dermal Toxicity Study In Rats, DACO: 4.2.2,IIA 5.2.2
2231617	2008, NOA449280 - 4 Hour Acute Inhalation Toxicity Study in Rats, DACO: 4.2.3,IIA 5.2.3
2231623	2007, NOA449280-Primary Skin Irritation Study In Rabbits (4-Hour Semi-Occlusive Application), DACO: 4.2.5,IIA 5.2.4
2231627	2007, NOA449280 - Primary Eye Irritation Study in Rabbits, DACO: 4.2.4,IIA 5.2.5
2231630	2008, NOA449280 - Local Lymph Node assay in the Mouse, DACO: 4.2.6,IIA 5.2.6
2231632	2003, NOA449280: 28 Day Oral Toxicity Study in Dogs, DACO: 4.3.3,IIA 5.3.1
2231634	2003, NOA449280_90 Day Dietary Toxicity Study in Rats, DACO: 4.3.1,IIA 5.3.2
2231636	2009, NOA449280 - 13 week rat dietary toxicity study, DACO: 4.3.1,IIA 5.3.2
2231638	2009, NOA449280 - 90 Day Mouse Preliminary Carcinogenicity Study, DACO: 4.3.1,IIA 5.3.2
2231642	2009, NOA449280 - 13-Week Oral (Capsule) Toxicity Study in the Beagle Dog, DACO: 4.3.2,IIA 5.3.3
2231646	2010, NOA449280 - 52-Week Oral (Capsule) Toxicity Study in the Dog, DACO: 4.3.2,IIA 5.3.4
2231649	2012, NOA449280 - Histopathology Changes in the Dorsal Root Ganglion of the Dog Following Dosing for 52 Weeks, DACO: 4.3.2,IIA 5.3.4
2231651	2009, NOA449280 - 28-Day Dermal Toxicity Study in the Wistar Rat, DACO: 4.3.5,IIA 5.3.7
2231653	2007, NOA449280 - Bacterial Mutation Assay In *S.typhimurium* And *E.coli*, DACO: 4.5.4,IIA 5.4.1
2231655	2010, Bicyclopyrone - *Salmonella Typhimurium* and *Escherichia Coli* Reverse Mutation Assay, DACO: 4.5.4,IIA 5.4.1
2231657	2006, NOA449280 - In Vitro Cytogenetic Assay In Human Lymphocytes, DACO: 4.5.6,IIA 5.4.2

2231659	2006, NOA449280 - L5178 TK+/- Mouse Lymphoma Mutation Assay, DACO: 4.5.5,IIA 5.4.3
2231661	2008, NOA449280 - Micronucleus Assay In Bone Marrow Cells Of The Rat, DACO: 4.5.7,IIA 5.4.4
2231663	2007, NOA449280 - In Vivo Rat Liver Unscheduled DNA Synthesis Assay, DACO: 4.5.8,IIA 5.4.5
2231665	2012, NOA449280 - 104 Week Rat Dietary Carcinogenicity Study with Combined 52 Week Toxicity Study, DACO: 4.4.1,4.4.2,4.4.4,IIA 5.5.1,IIA 5.5.2
2231666	2012, Review of the chronic toxicity of NOA449280 in rodents - Influence of the Mode of Action (HPPD inhibition), DACO: 4.4.2,4.4.4,IIA 5.5.2
2231668	2012, NOA449280 - 80 Week Mouse Dietary Carcinogenicity Study, DACO: 4.4.3,IIA 5.5.3
2231671	2007, NOA449280 - 14 day preliminary dietary toxicity study in rats, DACO: 4.8,IIA 5.5.4
2231673	2012, Bicyclopyrone - Effect on Rat Thyroid Peroxidase Activity In Vitro, DACO: 4.8,IIA 5.5.4
2231674	2012, Bicyclopyrone - 28 Day Dietary Thyroid Mode of Action Study in Rats, DACO: 4.8,IIA 5.5.4
2231677	Cartwright J., Green R., 2010, Tyrosine-derived 4-hydroxyphenylpyruvate reacts with ketone test fields of 3 commercially available urine dipsticks, DACO: 4.8,IIA 5.5.4
2231681	2009, NOA449280 - Oral (Dietary) Multigeneration Range Finding Study in the Rat, DACO: 4.5.1,IIA 5.6.1
2231684	2012, NOA449280 - Oral (Dietary) Multigeneration Study in the Rat, DACO: 4.5.1,IIA 5.6.1
2231686	2011, NOA449280 - Dose Range-Finding Prenatal Developmental Toxicity Study in the Han Wistar Rat, DACO: 4.5.2,IIA 5.6.10
2231688	2011, NOA449280 - Prenatal Developmental Toxicity Study in the Han Wistar Rat, DACO: 4.5.2,IIA 5.6.10
2231691	2007, NOA449280 - Dose Range Finding Study In The Pregnant Rabbit, DACO: 4.5.3,IIA 5.6.11
2231694	2012, NOA449280 - A Dose Range-Finding Prenatal Developmental Toxicity Study in New Zealand White Rabbits, DACO: 4.5.3,IIA 5.6.11
2231697	2012, NOA449280 - A Prenatal Developmental Toxicity Study in New Zealand White Rabbits, DACO: 4.5.3,IIA 5.6.11

2231700	2012, NOA449280 - Dose Range-Finding Prenatal Developmental Toxicity Study in the Himalayan Rabbit, DACO: 4.5.3,IIA 5.6.11
2231704	2012, NOA449280 - Prenatal Developmental Toxicity Study in the Himalayan Rabbit, DACO: 4.5.3,IIA 5.6.11
2231707	2012, NOA449280 - Prenatal Developmental Toxicity Study in the Himalayan Rabbit, DACO: 4.5.3,IIA 5.6.11
2231709	2012, NOA449280 - A Dose Range-Finding Prenatal Developmental Toxicity Study in New Zealand White Rabbits, DACO: 4.5.3,IIA 5.6.11
2231711	2012, NOA449280 - Development Toxicity Overview, DACO: 4.5.3,IIA 5.6.11
2231716	2012, NOA449280 - An Oral (Gavage) Acute Neurotoxicity Study in Rats, DACO: 4.5.12,IIA 5.7.1
2231718	2012, NOA449280 Technical - A Preliminary Acute Neurotoxicity Study of NOA449280 Technical in Rats, DACO: 4.5.12,IIA 5.7.1
2233219	2012, NOA449280/Mesotrione/Atrazine/S-Metolachlor/Benoxacor (A19707A) - Acute Oral Toxicity Up-and-Down Procedure in Rats, DACO: 4.6.1,IIIA 7.1.1
2233221	2012, Mesotrione/Atrazine/S-Metolachlor/Bicyclopyrone/Benoxacor ZC (A19707A) - Acute dermal toxicity in rats, DACO: 4.6.2,IIIA 7.1.2
2233223	2012, Mesotrione/Atrazine/S-Metolachlor/Bicyclopyrone/Benoxacor ZC (A19707A) - Acute inhalation toxicity in rats, DACO: 4.6.3,IIIA 7.1.3
2233225	2012, Mesotrione/Atrazine/S-Metolachlor/Bicyclopyrone/Benoxacor ZC (A19707A) - Primary skin irritation in rabbits, DACO: 4.6.5,IIIA 7.1.4
2233227	2012, Mesotrione/Atrazine/S-Metolachlor/Bicyclopyrone/Benoxacor ZC (A19707A) - Primary eye irritation study in rabbits, DACO: 4.6.4,IIIA 7.1.5
2233229	2012, Mesotrione/Atrazine/S-Metolachlor/Bicyclopyrone/Benoxacor ZC (A19707A) - Local Lymph Node Assay (LLNA) in mice, DACO: 4.6.6,IIIA 7.1.6
2234547	2010, NOA449280 SL (A16003E) - Acute Oral Toxicity Study in the Rat (Up and Down Procedure), DACO: 4.6.1,IIIA 7.1.1
2234549	2009, NOA449280 SL (A16003E) - Acute Dermal Toxicity Study in Rats, DACO: 4.6.2,IIIA 7.1.2
2234551	2010, NOA449280 SL (A16003E) - Acute Inhalation Toxicity Study (Nose-only) In The Rat, DACO: 4.6.3,IIIA 7.1.3
2234553	2010, NOA449280 SL (A16003E) - Primary Skin Irritation Study in Rabbits (4 Hour Semi-Occlusive Application), DACO: 4.6.5,IIIA 7.1.4

2234555	2009, NOA449280 SL (A16003E) - Primary Eye Irritation Study in Rabbits, DACO: 4.6.4,IIIA 7.1.5
2234557	2009, NOA449280 SL (A16003E) - Contact Hypersensitivity in Albino Guinea Pigs, Buehler Test (9-induction), DACO: 4.6.6,IIIA 7.1.6
2234438	2012, A16003E - Document MIII Section 3 - Toxicological Studies, DACO: 12.7,5.11,5.4,5.5,Document M,IIIA 7.3.3
2234558	2009, NOA449280 SL (A16003E) - In Vitro Absorption of NOA449280 Through Rat Epidermis, DACO: 5.8,IIIA 7.6.1
2234559	2009, NOA449280 SL (A16003E) - In Vivo Dermal Absorption Study in the Rat, DACO: 5.8,IIIA 7.6.1
2234560	2009, NOA449280 SL (A16003E) - In Vitro Absorption of NOA449280 Through Human Epidermis, DACO: 5.8,IIIA 7.6.2
2233152	2012, A19707A - Document MIII Section 3 - Toxicity and Metabolism Summary, DACO: 12.7,5.11,5.4,5.5,Document M,IIIA 7.3.3
2231733	2009, BICYCLOPYRONE - The Metabolism of BICYCLOPYRONE in Sugar Cane, DACO: 6.3,IIA 6.2.1
2231735	2010, BICYCLOPYRONE - The Metabolism of BICYCLOPYRONE in Maize, DACO: 6.3,IIA 6.2.1
2231738	2010, Metabolism of [14C]-BICYCLOPYRONE in the Laying Hen, DACO: 6.2,IIA 6.2.2
2231742	2010, [14C]-BICYCLOPYRONE - Metabolism in the lactating goat, DACO: 6.2,IIA 6.2.3
2231553	2012, NOA449280 - Residue Method (GRM030.03A) for the Determination of NOA449280 and Metabolite SYN503780 in crops, DACO: 7.2.1,7.2.4,7.2.5,IIA 4.3
2231554	2012, BICYCLOPYRONE - Analytical Method (GRM030.05A) for the Determination of Residues of BICYCLOPYRONE and Structurally Related Metabolites as the Moieties SYN503780 and CSCD686480 and for the Determination of CSAA806573 in Crop Matrices. Final determination by LC-MS/MS. 7.2.1, 7.2.4, IIA 4.3.
2231557	2012, NOA449280 - Independent Laboratory Validation of Method for GRM030.03A, NOA449280 - Residue Method for the Determination of NOA449280 and Metabolite SYN503780 in Crops, DACO: 7.2.1,7.2.2,7.2.3,7.2.4,IIA 4.3
2231558	2012, BICYCLOPYRONE - Independent Laboratory Validation of Method for GRM030.05A, BICYCLOPYRONE - Analytical Method for the Determination of Residues of BICYCLOPYRONE and Structurally Related Metabolites as the Moieties SYN503780 and CSCD686480 in Crop Matrices. 7.2.1, 7.2.4, IIA 4.3
2231559	2012, BICYCLOPYRONE - Independent Laboratory Validation of Method for GRM030.08A, BICYCLOPYRONE - Analytical Method for the Determination of Residues of BICYCLOPYRONE and Structurally Related Metabolites as the Moieties SYN503780 and CSCD686480 in Animal Tissues. Final determination by LC-MS/MS. 7.2.1, 7.2.4, IIA 4.3.

2231564	2012, BICYCLOPYRONE - Analytical Method (GRM030.08A) for the Determination of Residues of BICYCLOPYRONE and Structurally Related Metabolites as the Moieties SYN503780 and CSCD686480 in Animal Tissues. Final Determination by LC-MS/MS, DACO: 7.2.1,7.2.2,7.2.4,7.2.5
2231567	2012, BICYCLOPYRONE - Radiovalidation of Crop Residue Analytical Methods GRM030.03A, GRM030.05A and GRM030.09, DACO: 7.2.1,7.2.2,7.2.4,IIA 4.3
2231568	2010, [14C]BICYCLOPYRONE - Radiovalidation of Residue Analytical Method GRM030.08A, DACO: 7.2.1,7.2.2,7.2.4,IIA 4.3
2231569	2012, Magnitude of the residues in or on corn. 7.2.1, 7.2.4, 7.4.1, 7.4.2, 7.4.5, 7.4.6, IIA 4.3, IIA 6.3.1, IIA 6.5.3.
2231571	2012, BICYCLOPYRONE EC (A13765C) - Field Accumulation in Rotational Crops (90-, 150- and 270-Day PBI) USA, 2008, DACO: 7.2.1,7.2.4,7.4.4,IIA 4.3,IIA 6.6.3
2231727	2010, BICYCLOPYRONE - Storage Stability of BICYCLOPYRONE and its Metabolite SYN503780 Residues in Corn Grain, Straw, Spinach, Soybeans, Lentils, Citrus and Potatoes Stored Deep Frozen for up to Two Years., DACO: 7.3,IIA 6.1.1
2376141	Bicyclopyrone SL (A16003E)- Magnitude of the residues in or on corn USA 2012, DACO: 7.4.1,7.4.2,7.4.6,IIIA 8.3.1
2231751	2012, Determination of residues of bicyclopyrone (BICYCLOPYRONE) and its metabolites in sugarcane following the application of A16003E 200SL, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
2231755	2012, A16003 - Magnitude of residues of BICYCLOPYRONE and SYN503780 in sugarcane - Brazil, 2009-10, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
2231762	2012, Magnitude of Residues in Milk and Tissues of Dairy Cows Following Multiple Oral Administrations of BICYCLOPYRONE, DACO: 7.5,7.6,IIA 6.4.2
2231764	2010, BICYCLOPYRONE - Uptake and Metabolism in Confined Rotational Crops, DACO: 7.4.4,IIA 6.6.2
2231766	2012, BICYCLOPYRONE EC (A13765C) - Uptake in Rotational Wheat, USA, 2008, DACO: 7.4.4,IIA 6.6.3
2277280	2011, Determination of Residues of NOA449280 and SYN503780 in Vegetal Samples by LC/MS/MS Method, DACO: 7.2.1,7.2.4
2277281	2011, Determination of NOA449280, CSAA915194 and CSAA806573 Residues in Vegetable Samples by LC/MS/MS, DACO: 7.2.1,7.2.4
2294395	2013, BICYCLOPYRONE - Storage Stability of BICYCLOPYRONE in Eggs, Milk, Muscle and Liver under Freezer Storage Conditions, DACO: 7.3
2466394	2014, NOA449280 Analytical Method GRM030.05B for the Determination of Residues of NOA449280 and Structurally Related Metabolites as the Moieties SYN503780 and CSCD686480 in Crop Matrices, DACO: 7.2.1

2466395	2014, NOA449280 Analytical Method GRM030.08B for the Determination of Residues of NOA449280 and Structurally Related Metabolites as the Moieties SYN503780 and CSCD686480 in Animal Tissues, DACO: 7.2.1

3.0 Environment

2231454	2012, Bicyclopyrone MII Section 1 (GJR) - Identity, physical and chemical properties, further information and proposed classification, DACO: 1.1,12.7,2.1,2.10,2.2,2.3,2.3.1,2.4,2.5,2.6,2.7,2.8,2.9,Document M,IIA 1.1,IIA 1.2,IIA 1.3,IIA 1.4,IIA 1.5.1,IIA 1
2231767	2009, NOA449280 - Metabolism and Rate of Degradation of 14C bicyclooctenone Labelled NOA449280 under Aerobic Laboratory Conditions, in One Soil, at 20C, DACO: 8.2.3.4.2,IIA 7.1.1,IIA 7.2.1
2231768	2012, NOA449280 - Metabolism and Rate of Degradation of 14C bicyclooctenone Labelled NOA449280 under Aerobic Laboratory Conditions, in One Soil, at 20C, DACO: 8.2.3.4.2,IIA 7.1.1,IIA 7.2.1
2231769	2010, NOA449280 - METABOLISM AND RATE OF DEGRADATION OF 14C PYRIDINYL AND 14C BICYCLOOCTENONE LABELLED NOA449280 UNDER ANAEROBIC LABORATOTY CONDITIONS, IN ONE SOIL, AT 20C, DACO: 8.2.3.4.4,IIA 7.1.2,IIA 7.2.4
2231771	2012, 14C]NOA449280 - Photodegradation on Soil Surface, DACO: 8.2.3.3.1,IIA 7.1.3
2231773	2012, [14C]NOA449280 - Photodegradation on Three US Soils, DACO: 8.2.3.3.1,IIA 7.1.3
2231778	2008, NOA449280 - Rate of Degradation under Aerobic Laboratory Conditions in Two Soils at 20C, DACO: 8.2.3.4.2,IIA 7.2.1
2231779	2009, NOA449280 - Metabolism and Rate of Degradation of 14C-Pyridine Labelled NOA449280 under Aerobic Laboratory Conditions, in Five Soils, at 20C, DACO: 8.2.3.4.2,IIA 7.2.1
2231781	2009, NOA449280 - Rate of Degradation of NOA449280 under Aerobic Laboratory Conditions, in Five Soils, at 20C, DACO: 8.2.3.4.2,IIA 7.1.1,IIA 7.2.1
2231783	2009, NOA449280 - Metabolism and Rate of Degradation of 14C-pyridine Labelled NOA449280 under Aerobic Laboratory Conditions, in Seven US Soils, at 20C, DACO: 8.2.3.4.2,IIA 7.1.1,IIA 7.2.1

2231791	2010, NOA449280 - RATE OF DEGRADATION OF 14C-PYRIDINE LABELLED SYN503780, A SOIL METABOLITE, UNDER AEROBIC LABORATORY CONDITIONS, IN THREE SOILS, AT 20C, DACO: 8.2.3.4.2,IIA 7.2.3
2231794	2010, NOA449280 - Rate of Degradation of 14C-pyridine Labelled CSAA806573, a Soil Metabolite, under Aerobic Laboratory Conditions, in Three Soils, at 20C, DACO: 8.2.3.4.2,IIA 7.2.3
2231796	2011, Dissipation of NOA449280 EC Formulation in Bare Soil Plots Under Simulated Field Corn Production Conditions, DACO: 8.3.2,IIA 7.3.1
2231798	2011, Dissipation of NOA449280 250EC on Bare Soil Under Simulated Corn Production Conditions in Iowa, DACO: 8.3.2,IIA 7.3.1
2231799	2011, Dissipation of NOA449280 250EC on Bare Soil Under Simulated Corn Production Conditions in Nebraska, DACO: 8.3.2,IIA 7.3.1
2231819	2012, NOA449280 - Stability of NOA449280 and SYN503780 in Soil under Freezer Storage Conditions, DACO: 8.6,IIA 7.3.1
2231823	2012, Dissipation of 14C-NOA449280 EC Formulation in a Bare Soil Plot Under Simulated Field Corn Production Conditions, DACO: 8.3.2,8.6,IIA 7.3.1
2231825	2012, NOA449280 - Justification for a Waiver for a Reduction in North American Terrestrial Field Dissipation Study Locations, Specific to Canadian Ecozones, DACO: 8.3.2,IIA 7.3.1
2231826	2012, Stability of CSCC163768, CSCD656832, CSCD642512 and CSAA806573 in Soil Under Freezer Storage Conditions, DACO: 8.6,IIA 7.3.1
2231829	2010, NOA449280 - ADSORPTION AND DESORPTION PROPERTIES IN SEVEN SOILS, DACO: 8.2.4.2,IIA 7.4.1
2231831	2009, NOA449280 - Adsorption and Desorption Properties in Five Soils, DACO: 8.2.4.2,IIA 7.4.1
2231833	2009, NOA449280 - [14C]-NOA449280 - Adsorption and Desorption Properties in Two Soils, DACO: 8.2.4.2,IIA 7.4.1
2231836	2012, NOA449280 - Adsorption and Desorption Properties in Five Soils Taken from Field Study Sites, DACO: 8.2.4.2,IIA 7.4.1
2231837	2010, NOA449280 - Adsorption and Desorption Properties in Five Soils Taken from Field Study Sites, DACO: 8.2.4.2,IIA 7.4.1
2231839	2009, NOA449280 - ADSORPTION AND DESORPTION PROPERTIES OF [14C] SYN503780 IN FOUR SOILS, DACO: 8.2.4.2,IIA 7.4.2

2231841 2010, NOA449280 - Adsorption and Desorption Properties of [14C]CSAA806573 in Four Soils, DACO: 8.2.4.2,IIA 7.4.2

2231843 2009, NOA449280 - Adsorption and Desorption Properties of [14C]CSCC163768 in Four Soils, DACO: 8.2.4.2,IIA 7.4.2

2231845 2009, NOA449280 - ADSORPTION AND DESORPTION PROPERTIES OF [14C]CSCD656832 IN FOUR SOILS, DACO: 8.2.4.2,IIA 7.4.2

2231848 2012, [Pyridinyl-3-14C]-labelled NOA449280: Mobility and Degradation in Soil Outdoor Lysimeters, DACO: 8.2.4.6,IIA 7.4.7

2231850 2012, [Pyridinyl-3-14C]-labelled NOA449280: Mobility and Degradation in Soil Outdoor Lysimeters, DACO: 8.2.4.6,IIA 7.4.7

2231862 2012, NOA449280 - Determination of the Storage Stability of NOA449280 and its metabolites SYN503780, CSCC163768, CSCD656832, CSCD642512 and CSAA806573 in Groundwater, DACO: 8.2.4.6,IIA 7.4.8

2231864 2012, NOA449280 - Justification for a Waiver for Volatility and Phototransformation in Air Studies, DACO: 8.2.4.5,IIA 7.4.9

2231922 2011, NOA449280 - Waiver justification for fish bioaccumulation study, DACO: 9.5.6,IIA 8.2.6.1

2231868 2009, NOA449280 - [Pyridinyl-3-14C]-labelled NOA449280 - Metabolism and Rate of Degradation under Aerobic and Anaerobic Conditions in Aquatic Systems, DACO: 8.2.3.5.4,8.2.3.5.6,8.2.3.6,IIA 7.8.3

2231869 2010, NOA449280 - [Bicyclooctenone-6,7-14C]-labelled NOA449280 - Metabolism and Rate of Degradation under Aerobic and Anaerobic Conditions in Aquatic Systems, DACO: 8.2.3.5.4,8.2.3.5.6,8.2.3.6,IIA 7.8.3

2231871 2010, NOA449280-- - Route and Rate of Degradation in Water/Sediment Systems under Artificial Sunlight, DACO: 8.2.3.6,IIA 7.8.3

2231801 2012, NOA449280 - Soil Dissipation Study with A15749E, 150 EC, in or on Soil in Spain in 2007-2009, DACO: 8.3.2,IIA 7.3.1

2231803 2012, NOA449280 - Soil Dissipation Study with A15749E, 150 EC, in or on Soil in Italy in 2007-2009, DACO: 8.3.2,IIA 7.3.1

2231805 2012, NOA449280 - Soil Dissipation Study with A15749F, 150 EC, in or on Soil in Italy (site L01, Orzinuovi) - Multysite Study, DACO: 8.3.2,IIA 7.3.1

2231807 2012, NOA449280 - Soil Dissipation Study with A15749E, 150 EC, in or on Soil in Southern France in 2007 - 2008, DACO: 8.3.2,IIA 7.3.1

2231809 2012, NOA449280 - Soil Dissipation Study with A15749E, 150 EC, in or on Soil in Germany in 2007 - 2009, DACO: 8.3.2,IIA 7.3.1

2231811 2012, NOA449280 - Soil Dissipation Study with A15749F, 150 EC, in or on Soil in Northern France in 2008-2009, DACO: 8.3.2,IIA 7.3.1

2231813 2012, NOA449280 - Soil Dissipation Study with A15749F, 150 EC in or on Soil in Southern France, DACO: 8.3.2,IIA 7.3.1

2231815 2012, NOA449280 - Soil Dissipation Study with A15749F, 150 EC, in or on Soil in Lorsch, Germany, in 2008-2009, DACO: 8.3.2,IIA 7.3.1

2231817 2012, NOA449280 - Evaluation of Dissipation of Soil Residues of Experimental Herbicide Bicyclopyrone when Applied at the Rate of 300 g ai/ha to Simulated Sugar Cane Planting Field Conditions, Queensland, Australia, DACO: 8.3.2,IIA 7.3.1

2231821 2012, NOA449280 - Soil Dissipation Study with A15749F, 150 EC, in or on Soil in Hungary in 2008-2009, DACO: 8.3.2,IIA 7.3.1

2231852 2012, NOA449280 - Leaching Behaviour of NOA449280 and its Metabolite SYN503780 into Groundwater in a Field Trial - Lorsch, Germany, 2007-2012, DACO: 8.2.4.6,IIA 7.4.8

2231854 2012, NOA449280 - Leaching Behaviour of NOA449280 and its Metabolite SYN503780 into Groundwater in a Field Trial - Aba, Hungary, DACO: 8.2.4.6,IIA 7.4.8

2231856 2012, NOA449280 - Leaching Behaviour of NOA449280 and its Metabolite SYN503780 into Groundwater in a Field Trial - France, Alsace, DACO: 8.2.4.6,IIA 7.4.8

2231858 2012, NOA449280 - Field Leaching Study at Site L01 (Orzinuovi - BS) in Italy - Multisite Study, DACO: 8.2.4.6,IIA 7.4.8

2231860 2012, NOA449280 - Leaching Behaviour of NOA449280 and its metabolite SYN503780 into Groundwater in a Field Trial - Buzet-sur-Tarn, France, DACO: 8.2.4.6,IIA 7.4.8

2231938 2011, NOA449280 EC (A15749AD) - Toxicity to the aquatic higher plant Lemna gibba in a 7-day growth inhibition test, supplemented with testing for recovery of growth, DACO: 9.8.5,IIA 8.6

2263335 2009, NOA449280 - An acute oral toxicity study with the Canary (Serinus canaria), DACO: 9.6.2.1,9.6.2.2,9.6.2.3,IIA 8.1.1

2263338 2009, NOA449280 - An Acute Oral Toxicity study with the Northern Bobwhite, DACO: 9.6.2.1,9.6.2.2,9.6.2.3,IIA 8.1.1

2263341	2007, NOA449280 - A Dietary LC50 study with the Northern Bobwhite, DACO: 9.6.2.4,9.6.2.5,IIA 8.1.2
2263343	2007, NOA449280 - A Dietary LC50 study with the Mallard, DACO: 9.6.2.6,IIA 8.1.3
2263347	2008, NOA449280 - A reproduction study with the Northern bobwhite, DACO: 9.6.3.1,9.6.3.2,9.6.3.3,IIA 8.1.4
2263350	2009, NOA449280 - A reproduction study with the mallard, DACO: 9.6.3.1,9.6.3.2,9.6.3.3,IIA 8.1.4
2263352	2007, NOA449280 - Acute toxicity to fathead minnow (Pimephales promelas) in a 96-hour static test, DACO: 9.5.2.2,9.5.2.3,IIA 8.2.1.2
2263355	2008, NOA449280 - An early life-stage toxicity test to fathead minnow (Pimephales promelas), DACO: 9.5.3.1,IIA 8.2.4
2263358	2007, NOA449280 - Acute toxicity to Daphnia magna in a 48-hour immobilization test, DACO: 9.3.2,IIA 8.3.1.1
2263360	2008, NOA449280 - A 96-hour static acute toxicity test with the saltwater mysid (Americamysis bahia), DACO: 9.4.2,9.4.3,9.4.4,IIA 8.11.1
2263362	2008, NOA449280 - A 96-hour shell deposition test with the eastern oyster (Crassostrea virginica), DACO: 9.4.2,9.4.3,9.4.4,IIA 8.11.1
2263365	2008, NOA449280 - Effect on survival, growth and reproduction of Daphnia magna in a semi-static test over three weeks, DACO: 9.3.3,IIA 8.3.2.1
2263369	2007, NOA449280 - Toxicity to Pseudokirchneriella subcapitata (formerly selenastrum capricornutum) in a 96-hour algal growth inhibition test, DACO: 9.8.2,9.8.3,IIA 8.4
2263372	2008, NOA449280 - Toxicity to Anabaena flos-aquae in a 96-hour algal growth inhibition test, DACO: 9.8.2,9.8.3,IIA 8.4
2263376	2007, NOA449280 - Toxicity to Navicula pelliculosa in a 96-hour algal growth inhibition test, DACO: 9.8.2,9.8.3,IIA 8.4
2263379	2007, NOA449280 - Toxicity to the aquatic higher plant Lemna gibba in a 7-day semi-static growth inhibition test, DACO: 9.8.5,IIA 8.6
2263381	2007, NOA449280 - Acute oral and contact toxicity to the honeybee Apis mellifera L. in the laboratory, DACO: 9.2.4.1,9.2.4.2,IIA 8.7.1,IIA 8.7.2
2263383	2009, NOA449280 EC (A15749AD) - A rate-response laboratory bioassay of the effects of fresh residues on the parasitic wasp Aphidius rhopalosiphi (DeStephani-Perez) (Hymenoptera: Braconidae), DACO: 9.2.6,IIA 8.8.1.1
2263386	2009, NOA449280 - Acute toxicity to the earthworm Eisenia fetida, DACO: 9.2.3.1,IIA 8.9.1
2263389	2008, NOA449280 - A 96-hour acute toxicity test with the sheepshead minnow (Cyprinodon variegatus), DACO: 9.4.2,9.4.3,9.4.4,IIA 8.11.1
2263391	2008, NOA449280 - A 96-Hour Toxicity Test with the Marine Diatom (Skeletonema costatum), DACO: 9.8.5,IIA 8.6
2263394	2009, NOA449280 EC (A15749F) - Toxicity Effects on the Seedling Emergence of Terrestrial Non-Target Plant Species, DACO: 9.8.4,IIA 8.12
2263397	2009, NOA449280 EC (A15749F) - Toxicity Effects on the Vegetative Vigour of Terrestrial Non-Target Plant Species, DACO: 9.8.4,IIA 8.12
2263422	2009, NOA449280 EC (A15749AD) - A rate-response laboratory bioassay of the effects of fresh residues on the predatory mite Typhlodromus pyri (Acari:

	Phytoseiidae), DACO: 9.2.5,IIA 8.8.1.2
2263468	2009, CSCC163768 - Toxicity to the aquatic higher plant Lemna gibba in a 7-day growth inhibition test, DACO: 9.3.4,9.6.6,9.9,IIA 8.16.1
2263495	2009, CSAA589691 - Toxicity to then aquatic higher plant Lemna gibba in a 7-day growth inhibition test, DACO: 9.3.4,9.6.6,9.9,IIA 8.16.1
2263497	2009, NOA449280/S-metolachlor EC (A15936Z) - A rate-response extended laboratory bioassay of the effects of fresh residues on the parasitic wasp Aphidius rhopalosiphi (Hymenoptera: Braconidae), DACO: 9.2.6,IIA 8.8.2.1
2283600	2007, NOA449280 - ACUTE TOXICITY TO RAINBOW TROUT (ONCORHYNCHUS MYKISS) IN A 96-HOUR STATIC TEST, DACO: 9.5.2.1
2277403	2009, NOA449280 SL (200) (A16003E) - Acute toxicity to rainbow trout (Oncorhynchus mykiss) in a 96-hour test, DACO: 9.5.4,IIIA 10.2.2.1
2277407	2009, NOA449280 SL (200) (A16003E) - Acute toxicity to Daphnia magna in a 48-hour immobilization test, DACO: 9.3.2,IIIA 10.2.2.2
2277408	2009, NOA449280 SL (200) (A16003E) - Toxicity to Pseudokirchneriella subcapitata in a 96-hour growth inhibition test, DACO: 9.8.2,9.8.3,IIIA 10.2.2.3
2277412	2009, NOA449280 SL (A16003E) - Acute oral and contact toxicity to the honeybee Apis mellifera L. in the laboratory, DACO: 9.2.8,IIIA 10.4.2.1
2277414	2009, NOA449280 SL (A16003E) - Acute toxicity to the earthworm Eisenia fetida, DACO: 9.2.8,IIIA 10.6.2
2277418	2009, NOA449280 EC (A16003E) - An Acute Oral Toxicity Study with the Northern Bobwhite using a Sequential Testing Procedure, DACO: 9.6.4,IIIA 10.1.6

4.0 Value

PMRA Document Number	Reference
2234437	2012, A16003E - Document MIII Section 7 - Efficacy Data Summary, DACO: 12.7,Document M
2234545	Trial summary reports - Canada, DACO: 10.2.3.3,IIIA 6.1.2
2284055	2013, Syngenta Response to Value Clarification from the PMRA for SYNA16003 Herbicide and ACURON Herbicide, DACO: 0.8,10.1,10.2.1,10.3.1,10.3.2
2284057	Evaluate A19707A & B 412ZC, and SYNA16003E applied EPOST (1-2 LF) and SYNA16003E 200SN applied POST (5-6 LF) for true corn crop tolerance, DACO: 10.3.1,10.3.2

B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

PMRA Document Number	Reference
2115788	2008, Agricultural Reentry Task Force. Data submitted by the ARTF to Support Revision of Agricultural Transfer Coefficients

2.0 Environment

1573066 Atkins EL; Kellum D; Atkins KW, 1981. Reducing pesticide hazards to honey bees: mortality prediction techniques and integrated management techniques. Univ Calif, Div Agric Sci, Leaflet 2883. 22 pp.

1918520 Cohen, S.Z., S.M. Creeger, R.F. Carsel and C.G. Enfield, 1984. Potential for pesticide contamination of groundwater resulting from agricultural uses. Pages 297-325 In R.F. Krugger and J.N. Seiber, eds., Treatment and Disposal of Pesticide Wastes. ACS Symposium Series No. 259. American Chemical Society, Washington, DC, pp. 297-325.

2439880 Crailsheim, K., Schneider, L.H.W. Hrassnigg, N., Buhlmann, G. Brosch, U., Gmeinbauer, B., Schoffmann, B. 1992. Pollen Consumption and Utilization in Worker Honeybees (Apis melifera carnica): Dependence on Individual Age and Function. J. Insect Physiol. Vol. 38, No. 6, 409-419, 1992

2439881 Crailsheim, K., Hrassnigg, N.,Gmeinbauer, B., Szolderits, M.J., L.H.W. Schneider, Brosch, U.1993. Pollen Utilization in Non-Breeding Honeybees in Winter. J. Insect Physiol. Vol. 39, No. 5, 369-373, 1993

2439879 De Snoo, G.R. and R. Luttik, 2004. Availability of pesticide-treated seed on arable fields. Pest Management Science 60:501-506.

1918522 Fletcher, J.S., Nellessen, J.E., and Pfleeger, T.G., 1994. Literature review and evaluation of the EPA food-chain (Kenaga) nomogram, an instrument for estimating pesticide residues on plants. Environmental Toxicology and Chemistry 13:1383-1391.

Ganzelmeier, H; Rautmann, D; Spangenberg, R; Streloke, M; Herrmann, M; Wenzelburger, H-J; Walter, H-F 1995. Studies on the spray drift of plant protection protection products: Results of a test program carried out throughout the Federal Republic of Germany. Report Number 305 from the Biologischen Bundesanstalt fur Land-und Forstwirtschaft, Berlin-Dahlem. Blackwell Wissenschafts-Verlag GmbH, Berlin/Vienna.

1918524	Gustafson, D.I., 1989. Groundwater ubiquity score: a simple method for assessing pesticide leachability. Environmental Toxicology and Chemistry, v. 8, no. 4, p. 339-357.
1918526	Hoerger F; Kenaga EE., 1972. Pesticide residues on plants: correlation of representative data as basis for estimation of their magnitude in the environment. In: Coulston F; Korte F. (eds). Global aspects of chemistry, toxicology and technology as applied to the environment, Vol. I. Thieme, Stuttgart, and Academic Press, New York. pp. 9-28.
1918527	Kenaga EE., 1973. Factors to be considered in the evaluation of the toxicity of pesticides to birds in their environment. In: Coulston F; Dote F. (eds). Global aspects of chemistry, toxicology and technology as applied to the environment, Vol. II. Thieme, Stuttgart, and Academic Press, New York. pp. 166-181.
2439884	Koch, H. and Weiber, P. 1997. Exposure of honey bees during pesticide application under field conditions. Apidologie (1997)28, 439-447
2024011	McCall, P.J., Laskowski, D.A., Swann, R.L. and Dishburger, H.J., 1981. Measurements of sorption coefficients of organic chemicals and their use in environmental fate analysis. In Test Protocols for Environmental Fate and Movement of Toxicants. Proceedings of AOAC Symposium, AOAC, Washington D.C.
1918529	Nagy, K.A., 1987. Field metabolic rate and food requirement scaling in mammals and birds. Ecological Monographs 57:111-128.
2439883	Rortais, A.; Arnold, G.; Halm, M-P.; Touffet-Briens, F., 2005. Modes of honeybees exposure to systemic insecticides: estimated amounts of contaminated pollen and nectar consumed by different categories of bees
2439872	Urban DJ; Cook NJ., 1986. Hazard Evaluation Division, Standard Evaluation Procedure, Ecological Risk Assessment. EPA 540/9-85-001. US EPA, Washington, DC.
2439935	Wolf, T.M. and Caldwell, B.C., 2001. Development of a Canadian spray drift model for the determination of buffer zone distances. In Expert Committee on Weeds - Comité d'experts en malherbologie (ECWCEM), Proceedings of the 2001 National Meeting, Québec City. Sainte-Anne-de-Bellevue, Québec: ECW-CEM. Eds. D Bernier, D R A Campbell and D Cloutier, pp. 60.

3.0 Value

PMRA Document Number	Reference
2311840	2008, Bollman, J.D., C.M. Boerboom, R.L. Becker and V.A. Fritz, Efficacy and tolerance to HPPD-inhibiting herbicides in sweet corn, Weed Technology 22:666-674.
2311841	2002, O'Sullivan, J., J. Zandstra and P Sikkema, Sweet corn (*Zea mays*) cultivar sensitivity to mesotrione, Weed Technology 16:421-425.
2311842	2001, O'Sullivan, J., R.J. Thomas and P Sikkema, Sweet corn (*Zea mays*) cultivar sensitivity to RPA 201772, Weed Technology 15:332-336.
2311843	2007, Soltani, N., P.H. Sikkema, J. Zandstra, J. O'Sullivan and D.E. Robinson, Response of eight sweet corn (*Zea mays* L.) hybrids to topramezone, HortScience 42(1):110-112.